**UNITED STATES OF AMERICA**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**PUBLIC HEALTH SERVICE**

**FOOD AND DRUG ADMINISTRATION**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

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# DRUG ABUSE ADVISORY COMMITTEE

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**MEETING**

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**TUESDAY,**
**FEBRUARY 11, 1997**

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**The committee met in the Ballroom, Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland at 9:00 a.m., MAX A. SCHNEIDER, M.D., CADC, Chair, presiding.**

**PRESENT:**

**MAX A. SCHNEIDER, M.D., CADC, Chair**
**KIMBERLY TOPPER, M.S., Executive Secretary**
**SUSAN A. COHEN, Consumer Representative**
**HARRIET de WIT, M.D.**
**CAROL L. FALKOWSKI**
**ELIZABETH KHURI, M.D.**
**LLYN A. LLOYD, R.Ph.**
**ERIC C. STRAIN, M.D.**
**ALICE M. YOUNG, Ph.D.**

**FDA REPRESENTATIVES:**

**WILEY A. CHAMBERS, M.D.**
**MICHAEL KLEIN, Ph.D.**
**CURTIS WRIGHT, M.D.**

**SPEAKERS:**

**TIM BENEDICT, R.Ph.**
**SILVIA N. CALDERON, Ph.D.**
**DALE CONNER, Pharm.D.**
**KIRA HUTCHINSON, Ph.D.**
**MICHAEL KAPLAN, M.D., Ph.D.**
**ARTHUR RAINES, Ph.D.**
**PETER STAATS, M.D.**

**JAMES COSTIN, M.D., Sponsor Presenter**

**ALSO PRESENT:**

**HARRY FLANAGAN, D.O.**
**LOUIS HARRIS, Ph.D.**
**SOLOMON STEINER, Ph.D.**

# I-N-D-E-X

# I-N-D-E-X (Continued)

P-R-O-C-E-E-D-I-N-G-S

(9:02 a.m.)

GREETING AND CALL TO ORDER

CHAIRMAN SCHNEIDER: Good morning. I am going to call this meeting to order. My name is Max Schneider. And I would like to introduce Ms. Kimberly Topper, the Executive Secretary.

EXECUTIVE SECRETARY TOPPER: And after he introduced me, I'd like to introduce to you all the new Executive Secretary for this Committee. She'll be taking over as soon as the meeting is over today. That's Karen Somers. Karen, would you stand up, please, so everybody can see you? She'll be the one you all want to call in the future.

CONFLICT OF INTEREST STATEMENT

EXECUTIVE SECRETARY TOPPER: This is a conflict of interest statement. "This following announcement addresses the issue of conflict of interest with regard to this meeting and is made part as of the record to preclude even the appearance of such at this meeting.

"Based on the submitted agenda for the meeting and all financial interest reported by the committee participants, it has been determined that all interests in firms reported by the participants

present no potential for an appearance of conflict of interest at this meeting with the following exceptions.

"In accordance with 18 USC Section 208(b)(3), full waivers have been granted to: Dr. Max Schneider and Mrs. Susan Cohen. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

"In the event the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement. And their exclusion will be noted for the record.

"With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon."

Thank you.

CHAIRMAN SCHNEIDER: Thank you very much.

I'd like now to introduce or have each individual introduce herself/himself for the Committee. Let me start with Dr. Wright this morning, who is not on the Committee.

Dr. Wright?

OPENING REMARKS AND INTRODUCTION

DR. WRIGHT: Curtis Wright. I'm the Acting Director of HFD 170, the review division at the FDA that deals with addition drug products.

DR. KLEIN: I'm Michael Klein. I'm the Acting Team Leader for Controlled Substances within the division that Dr. Wright is the division director of.

DR. CHAMBERS: Wiley Chambers. I'm the Acting Director for the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products.

CHAIRMAN SCHNEIDER: Dr. Khuri?

DR. KHURI: Elizabeth Khuri from New York City, Associate Professor of Public Health in Pediatrics, Cornell and a position at Rockefeller University.

DR. YOUNG: Alice Young, Professor of Psychology, Wayne State University, Detroit.

CHAIRMAN SCHNEIDER: You've met Ms. Topper. My name is Max Schneider. I'm a physician, internist, gastroenterologist, by appointment a Clinical Associate Professor of Psychiatry. I am medical director of a nonprofit treatment center in Orange, California, past President of ASAM, and

currently the Deputy Chair of the National Council on Alcoholism and Drug dependence.

MS. COHEN: I'm going to feel very self-conscious. I'm the consumer member, Susan Cohen. I have nothing to say.

CHAIRMAN SCHNEIDER: You said it all.

DR. de WIT: I'm Harriet de Wit from the University of Chicago.

MR. LLOYD: I'm Llyn Lloyd from the Arizona State Board of Pharmacy.

MS. FALKOWSKI: I'm Carol Falkowski with the Minnesota State Alcohol and Drug Abuse Agency.

DR. STRAIN: I'm Eric Strain. And I'm from Baltimore, Maryland.

CHAIRMAN SCHNEIDER: I'm going to try and keep us on a time schedule today. It looks like a full day. I do not like to cut off debate, but keep your eyes on this, ladies and gentlemen, please, because we do want to facilitate this as nicely as possible and as gently as possible.

I think our opening remarks this morning will be by both Dr. Michael Klein and Dr. Curtis Wright. I don't know which is going first. Dr. Wright?

DR. WRIGHT: For those of you who are new

to the Committee, this is a typical Drug Abuse Advisory Committee problem. Soma is an old drug, but it may have developed a pattern of diversion into illicit use in a subpopulation of alcohol and drug-abusing individuals.

The purpose of this meeting is to present the Committee with the request for a scheduling determination sent to us by the DEA, to present the information held by the agency and at least one sponsor, and to ask the Committee what additional data, if any, it recommends we develop to render a proper scientific opinion in this case.

We expect it to take at least several months to develop such information as you may require, if you do. And it is our plan to bring this information back to the Committee for a final recommendation at a future time, if necessary.

Your job today is to review what is known and to ensure that we ask for the right data so that we may make a sound decision. Again, Dr. Klein will now talk about some of the kinds of information that we need to make a proper scheduling decision.

CHAIRMAN SCHNEIDER: Dr. Klein?

DR. KLEIN: As the Committee has seen in the package of material, Soma was approved in 1959.

In 1996 we received a request from the Drug Enforcement Administration to schedule it. There has been some increasing use of the drug, although there have been no new indications that the drug has been approved for.

Some of the issues that we feel have to be addressed -- and we've started putting together our review -- relate to the state of the current science as far as how this drug is viewed. It reportedly metabolizes to meprobamate. And this is its active metabolite.

We have to look at some of the adequacy of the studies that have been conducted thus far and look at the abuse liability studies, in particular, because most of the studies have been conducted on meprobamate and not on Carisoprodol itself. So there might be an inference that the meprobamate is indeed responsible for the effects of the Carisoprodol elicits.

Also, we have to look at the current clinical role for the drug and how it is used in practice. And this is important because as we look at the available abuse-indicating data, we need to have a clear separation of abuse issues versus misuse issues and, in fact, make that distinction and see if we can deal with reported problems of abuse possibly

through product labeling rewrites.

In looking at the available actual abuse-indicating data, we don't really have one system that indicates a problem in and of itself. We're looking at a variety of data systems that are available to us, and we're looking for consistency across those data systems or if we can't find consistency at least to be able to explain why we see differences among them.

Primarily we have been looking at Drug Abuse Warning Network, the DAWN data system, and FDA's MEDWATCH system, which analyzes adverse drug reactions. Dr. Calderon later will expand on some of the details of the numbers we've seen and explain the issues involved with those systems.

Finally, we have had the issue of identification of the proper comparator drugs to use against Carisoprodol. And for those, we're primarily relying on meprobamate and diazepam, although there are problems built into use of either one of those drugs as a positive comparator. And, again, Dr. Calderon will go into those in more detail later.

Could I have the next slide, please? And in making a drug scheduling recommendation, we have to address these eight factors, which are listed in the

Controlled Substances Act, that run the gamut from scientific issues, pharmacology, medical use, to actual abuse indication, to a discussion of what the public health impact is that abuse of the drug will lead to.

Thank you.

CHAIRMAN SCHNEIDER: Any questions from the Committee?

(No response.)

CHAIRMAN SCHNEIDER: Thank you, Doctor.

I must make a comment that any time anybody is going to get up to speak, please use a microphone. I think there's one standing back there and, of course, one up here. And we can lend one from the table any time.

I'd like to call upon now Dr. Kira Hutchinson. She's a drug scientist specialist from the Drug and Chemical Evaluation Section, Office of Diversion Control.

(Pause.)

CHAIRMAN SCHNEIDER: The suspense is overwhelming.

DR. HUTCHINSON: Sorry.

DR. WRIGHT: You're among friends.

DR. HUTCHINSON: Thank you.

**DRUG ENFORCEMENT ADMINISTRATION**

**CARISOPRODOL ACTUAL ABUSE DATA**

**DR. HUTCHINSON: I'm going to present data today that comes from STRIDE, the system to retrieve information from drug evidence, and associated federal investigative reports. They will present diversion and trafficking data that is indicative of actual abuse of Carisoprodol. And I'll be looking at the period of time from 1980 to 1996.**

**I would like to describe the STRIDE database. It is the system to retrieve information from drug evidence. This is a database that provides information about drug exhibits submitted to DEA laboratories for analysis.**

**It documents numerous information about the seizures or the encounters with these drugs, such as the date, the place, and the method for acquiring the substance, its price, chemical analysis, and the form in which it was received.**

**This is an actual reporting database. And it reflects trends in federal law enforcement priorities, which are, of course, for controlled substances. And for this, it's important to understand that non-controlled substances tend to be under-reported.**

It captures very little information provided from state and local law enforcement offices. And when it is used in combination with federal investigative reports, this information documents that the drug is encountered in the illicit traffic.

I would like to summarize what we have found out from the STRIDE database and overall from 1980 to 1986. It encountered 224 times. A total of roughly 72,000 tablets have been analyzed containing Carisoprodol.

It's been encountered throughout the United States, 27 states and the District of Columbia. Most of the encounters of Carisoprodol in STRIDE involve seizures, either from residents during the execution of a search warrant or a pharmacy or a medical establishment that is under investigation.

Twenty-seven percent of the encounters have been undercover purchases, where someone has said, "I've got this drug here. I'd like you to try it." And then it was found out later on that it was Carisoprodol.

Sometimes it was a free gift, five percent of the times. And, most notably, Carisoprodol is encountered in situations where other controlled substances are diverted and trafficked.

The STRIDE database documents that Carisoprodol has been represented as methaqualone in the illicit drug market. And I'm going to talk about two cases.

In 1982, an individual was arrested. it was part of an undercover investigation in the trafficking of methaqualone. When this person was arrested, 10,000 tablets were seized. Nine hundred of them were actual methaqualone, and 9,000 turned out to be Carisoprodol, as determined by laboratory analysis.

Again in 1982, another seizure of suspected methaqualone occurred. In this case, it was 40,000 tablets. And, as another part of this investigation, an investigator agent received 990 suspected methaqualone tablets. What was unusual about these was they had the markings "Lemmon 714," which was indicative of a brand of methaqualone at that time, but laboratory analysis showed that these only contained Carisoprodol.

And this is a very large seizure of tablets. The data implies that Carisoprodol tablets were either being grown up and then reprocessed to resemble methaqualone or, else, a bulk powder was being diverted and then retableted on a very large scale.

I would also like to indicate that similar cases have been encountered in other areas besides Miami and New Jersey, demonstrating that this is not an isolated problem.

The STRIDE database also documents that Carisoprodol is diverted from clinics. In most cases, these clinics are dubbed the name "prescription mill." They're less-than-desirable places. Usually they don't have running water. It's a very interesting establishment. And usually there's a collaborating pharmacy with this establishment.

Often people go in there and they are paying on a cash basis. And the doctor in charge will document that they have received services and charge the patient for these services, but they do not receive these services.

They're then given a prescription for a medication, which is often a controlled substance. And the doctor will issue the medication from that establishment or refer the person to a specific pharmacy. Often the reason for the referral is that other pharmacies will not fill this doctor's prescriptions.

DEA has documented the diversion data from these places involving Carisoprodol because they've

received complaints about controlled substances. And it's just that the Carisoprodol was basically documented along for the ride. It wasn't a priority.

The STRIDE data and associated federal investigative files demonstrate that Carisoprodol is often obtained in combination with narcotic analgesics, such as Tylenol with codeine.

And the diversion of Carisoprodol is very similar to other controlled substances, the manner in which it is diverted and also the fact that it's combined with a narcotic analgesic. It's very reminiscent of the diversion of glutethimide.

It has been noted, a lot of diversion investigators have reported to me or have noted, that areas where Carisoprodol is prescribed the most correspond with areas where physicians have lost their DEA registration to prescribed controlled substances. And this has been documented on the state level as well.

Recently -- and this information is not provided in the Eight Factor Analysis -- I obtained the prescription records from a doctor that was under investigation in western New York State.

This doctor was the largest prescriber of controlled substances in that area. He was known to

be diverting substances. His patients were all known drug abusers. And he's under investigation for prescription fraud from the state. Many pharmacies in the area refused to fill his prescriptions.

It's not often that I get the chance to look at someone's prescriptions. And I took this opportunity just for my own evaluation because it's known and it's been documented in the federal investigative file that Carisoprodol is often combined with Tylenol with codeine or is prescribed in that combination. And I wanted to see if this doctor's prescriptions were similar.

I want to also point out before I go into this any further that his prescriptions were pulled, investigated, and Carisoprodol was pulled as well because in this area, western New York State, Carisoprodol is considered a significant problem of abuse that they are now actually taking the time to document the abuse of this substance.

This doctor had prescribed numerous controlled substances. I looked at a six-month period of time, and I found that he had prescribed Carisoprodol over 73 times. And of those 73 times, 53 times it was with Tylenol with codeine. And of those 53, he also prescribed Tylenol with codeine and

Valium. And 13 of those 53 times, it was Tylenol with codeine, Carisoprodol, Valium, and one or two other controlled substances. And then less often, Carisoprodol was prescribed alone. And sometimes more than one prescription would be issued at one time.

The STRIDE database also documents that Carisoprodol is diverted from pharmacies. We have cases where pharmacists have been giving Carisoprodol to individuals or have been selling it without a prescription.

Shortages of Carisoprodol have been documented. One pharmacy in Detroit found for an audit in August they were short 20,000 tablets. And it was confirmed that the pharmacist had been selling the drug.

Carisoprodol has been purchased for cash during undercover investigations. And there are documents of thefts and armed robberies where Carisoprodol and Tylenol IV are the drugs that are demanded. And this is also widespread. The diversion from pharmacies has occurred in numerous states.

The STRIDE database and federal investigative reports have established that Carisoprodol is trafficked in the United States. It has a street value.

There are street names for Carisoprodol combined with codeine products, such as baby loads, which, again, is reminiscent of the glutethimide and codeine combinations.

We have evidence that Carisoprodol is brought into the United States from Mexico. We have reports in the federal investigative files that are also corroborated by states, state reports, that pharmacies have begun to not fill prescriptions for Carisoprodol because they know that it's only for purposes of abuse.

It's found in the possession of people who are dealing and trafficking in other controlled substances. And the generic and name brand products have all been encountered.

I think this is additional evidence since I submitted the Eight Factor Analysis. Recently a joint investigation with FDA, DEA, Baja, California health officials and DEA have documented that two million Carisoprodol tablets were purchased by Tiajuana pharmacists from American pharmaceutical companies during a four-month period in 1996.

These tablets were taken across the border, and they were not declared by Customs. It is believed that these tablets are intended for American

tourists in the Tiajuana area because they're only sold in a stretch of Tiajuana that is called the tourist area. And in these pharmacies, there are about 120 pharmacies that cater to American tourists in this area.

It is also believed that they are intended for Americans because of the fact that Carisoprodol is not sold in any other part of Tiajuana and the drug is more expensive than can be afforded by the local.

This data is also corroborated by the fact that in the federal investigative files we have other places where people have indicated that they are selling Carisoprodol and that large doses are being acquired from Mexico and they're brought in on a regular basis.

It's interesting that Carisoprodol and Butalbital are the major substances acquired by these pharmacies in terms of tablets and monetary value.

This is recent information as well. And I don't know if this is a trend or not, but we are finding Carisoprodol combined with other controlled substances in some cases, there have been seizures of heroin that are actually procaine and Carisoprodol. Cocaine and Carisoprodol poly are being encountered. These are all recent, very recent. And heroin,

cocaine, and Carisoprodol is being sold as heroin on the streets.

Now, this is interesting because if you look at the recent medical examiner's data, in 1994, I believe there were -- if you look at the drugs found along with Carisoprodol in these reports, 14 percent of the cases involved heroin, but in 1995 it was 29. So there was a big jump. And that's just one data point right now. So it's highly speculative as to what is going on. But I wanted to make sure that you got my point.

The federal data document some indications of abuse. Carisoprodol is being sought by doctor shoppers or people who go from doctor to doctor until they find one that will give them the medication that they so desire.

A lot of times -- no. A lot of times there are indications that people are receiving multiple prescriptions from multiple physicians for Carisoprodol. There are indications that it is taken at elevated doses or overdose has occurred.

We have examples of Carisoprodol obtained by fraudulent or altered prescriptions. And, again, it is abused in combination with narcotic analgesics and more often anxiolytics. We have evidence that

it's being used to assuage withdraw from cocaine or other controlled substances.

There are also indications that it is abused for the effects of Carisoprodol in itself. And we also have evidence that it is being smuggled into prisons and it's being ground up and laced into cigarettes and smoked, although most of our indications of abuse indicate that it is occurring by oral administration.

As I pointed out in the beginning, the federal information is incomplete. However, I want to also indicate that we have received information from state agencies. And the data from these agencies tend to corroborate the federal investigative reports.

Again, it is diverted. In certain areas, it is the drug of choice. And most often the reason that people indicate that it is the drug of choice is that it is easy to obtain.

Again, the states document that it is obtained by prescription fraud and doctor shopping. And it is prescribed in combination with hydrocodone and other narcotic analgesics. It's also used to ease the crash of controlled substances. And sales are highest in areas where DEA registrations have been revoked.

Again, the states indicate that pharmacists are beginning to refuse to fill prescriptions for Carisoprodol, especially those that are phoned in, because they are often fraudulent.

We have also received several phone calls and letters from concerned physicians stating that they are seeing drug-seeking behavior for Carisoprodol and that there is some intimidation of doctors to write prescriptions for Carisoprodol and Tylenol. They're reporting overdose and dependence.

And we have received recommendations from boards of pharmacy and a national association of state-controlled substances that we consider the control of this substance. And there are five states that have controlled Carisoprodol in this nation.

I'd like to conclude by stating that the database documents that Carisoprodol is trafficked and diverted in this country, which are indications that it has abuse potential, I would like to reiterate that non-controlled substances tend to be under-reported. So any data that we have is significant.

I would like to make sure that you understand that the encounters are widespread. It's not a local problem. It's been represented as a controlled substance. The diversion and the use are

similar to controlled substances. It's encountered in places where controlled substances are trafficked. And our data is corroborated by other sources of information, state and local data.

And that's it.

CHAIRMAN SCHNEIDER: Thank you, Dr. Hutchinson.

Any questions of Dr. Hutchinson?

MS. FALKOWSKI: Yes. I have a question. In the materials you sent us, you stated based on the STRIDE data, that these data do not necessarily reflect a trend of increased Carisoprodol use. Does what you presented since the information we have in here lead you to a different conclusion?

DR. HUTCHINSON: I would not rely on the STRIDE data to show a trend in increase. I would use multiple indicators of drug abuse to draw that conclusion.

At this time I know that Dr. Calderon and other people will be presenting the medical examiner's data and the DAWN data. I think it's best if you use the STRIDE data in conjunction with those to draw the conclusion of whether or not there is an increase.

The STRIDE data is not a statistical database. It's what law enforcement people are

concentrating on in that area. For example, I might get a case and I would see that diazepam and hydrocodone are being reported. I might have to call that investigator and say, "Are you seeing Carisoprodol?"

And they'd say, "Well, let me check," see, because it's not being reported because it's not controlled.

MS. FALKOWSKI: Right. I am aware of the indications of the database. I'm simply trying to determine: Since the information that we received talked about a total of 144 STRIDE encounters of it through '94 and now in '96 it has risen to 224, I am asking if the conclusion that you reached that this does not necessarily reflect a trend of increased use is still the case or based on your new information, do you change that conclusion?

DR. HUTCHINSON: I would conclude that on the basis of the STRIDE data, I cannot show that there is an increased abuse.

MS. FALKOWSKI: Okay.

CHAIRMAN SCHNEIDER: Increased reporting versus increased use.

MS. FALKOWSKI: Right. Thank you.

CHAIRMAN SCHNEIDER: Ms. Cohen?

MS. COHEN: Is this being made in garages or where is the source of the drug?

DR. HUTCHINSON: We have no reports that this substance is being synthesized clandestinely. It is mostly that prescriptions are easy to obtain. And that is the route by which --

MS. COHEN: That is the major route by which --

DR. HUTCHINSON: Yes.

MS. COHEN: Okay. Thank you.

CHAIRMAN SCHNEIDER: Doctor?

DR. KLEIN: Do you have a breakdown that describes the individuals who are using the drug, the motivations, the age, gender?

DR. HUTCHINSON: I did a breakdown on the basis of the DAWN data. And it was found more often than not middle-aged women tended to use Carisoprodol more than men.

DR. KLEIN: That's the group that's abusing the drug?

DR. HUTCHINSON: On the basis of the DAWN data. With the STRIDE data, it's mixed. It's hard to say if someone is getting a prescription whether they are using it or they are selling it or they have a legitimate, for that matter.

CHAIRMAN SCHNEIDER: Dr. Wright?

DR. WRIGHT: In your analysis, more often than not, this was traveling with other drugs known to be diverted in terms of the pattern of prescription and usage?

DR. HUTCHINSON: In terms of how it's abused or how it's obtained.

DR. WRIGHT: How it's obtained.

DR. HUTCHINSON: How it's obtained? It's often obtained with a narcotic analgesic or a benzo.

DR. YOUNG: Can you for background information give me some idea of what other kinds of non-schedule drugs are encountered under these conditions?

DR. HUTCHINSON: Stadol, nubain.

DR. YOUNG: I understand that there has been some concern over agents such as clonidine, which are encountered at traffick along with drugs of abuse. The suggestion has been that the use of clonidine is not for as itself a drug of abuse but is being used as perhaps an adjunct withdrawal.

Can you differentiate between Carisoprodol and a drug such as clonidine, which, at least is some databases, is co-mentioned with drugs of abuse?

DR. HUTCHINSON: We have indications that

Carisoprodol is used to enhance the effects of a narcotic analgesic. We also have reports that it is used alone.

DR. YOUNG: Can you indicate what kind of information draws you to the conclusion it's being used to enhance?

DR. HUTCHINSON: This comes from statements from people who are abusing the substance. And it's indicated in the files. This comes from DAWN data, medical examiner's data. It comes from reports from physicians, pharmacists, many sources.

DR. YOUNG: And how often is Carisoprodol encountered alone?

DR. HUTCHINSON: Less frequently than with the narcotic analgesic.

DR. YOUNG: Can you give me an idea of the other groups of compounds that would be in its class? Did you look at it alone?

DR. HUTCHINSON: I'm sorry. Could you repeat that?

DR. YOUNG: What other kinds of compounds would show the same pattern on single encounters, encounters alone?

DR. HUTCHINSON: I'm not sure I understand what you're asking.

CHAIRMAN SCHNEIDER: Just for the record, DAWN means Drug Abuse Warning Network.

Thank you very much, Dr. Hutchinson.

Any further questions?

(No response.)

CHAIRMAN SCHNEIDER: May I introduce, then, Mr. Tim Benedict from the Ohio State Board of Pharmacy. Mr. Benedict?

MR. BENEDICT: Good morning. My name is Tim Benedict. I am the Compliance and Enforcement Administrator for the Ohio State Board of Pharmacy. The Board of Pharmacy in Ohio is both a licensing, regulatory agency and we are also a law enforcement agency.

I have been requested by DEA to come here today to share with you the experiences that Ohio has had with the diversion of Carisoprodol. I'd like to state up front that DEA did request my presence here today. I am testifying in their behalf. And they have paid for my travel to come down here.

Since 1987, the Board of Pharmacy has investigated 65 cases that have involved the diversion of Carisoprodol. These 65 cases documented the diversion of 424,360 doses of Carisoprodol. The diversion of this drug is the result of a combination

of thefts, forged prescriptions, doctor shopping, and straight illegal sales.

I'd like to point out that because of limited manpower with the Board of Pharmacy, we deal mostly with health care professionals in illegal activity. The local police departments, sheriff's departments usually deal with the street people.

But if you look at the 65 cases, the majority of them are small in number as far as quantity goes. However, when you get into the health care professionals, it's a different story.

The most aggravated of these cases was a physician who had lost his DEA license due to criminal charges in two other states. He still had a medical license in a bordering state of Ohio.

He was arrested selling Carisoprodol from a motel room in southwest Ohio. At the time of his arrest, he had approximately $99,000 in cash and 100,000 dosage units of the drug in his possession.

A search of his car and finding that he had a storage locker and a search of that storage locker found empty bottles which accounted for 44,500 additional doses of this drug.

Through invoices and other records that were seized, it was finally determined that during his

tenure in southwest Ohio, he had purchased approximately 280,000 dosage units of this drug.

We have also had two other cases where physicians once they have surrendered their DEA licenses but still had their medical licenses for a short period of time immediately went and starting writing a large number of prescriptions for Carisoprodol.

Another physician in northwest Ohio, we documented an investigation on him that he had written prescriptions for approximately 14,950 dosage units of the drug for non-legitimate medical purposes. This was in combination with narcotic and amphetamine substances also.

There have been four major investigations of pharmacists during this time period where the diversion of Carisoprodol was of significant quantity. These four cases have accounted for 94,057 dosage units of this drug being diverted into the illegal market.

Three of these cases, the majority of it was illegal prescriptions, forging of prescriptions, to cover for the doses that were put into the illegal market. One of these cases was an outright trafficking case. All four of these pharmacists have

been convicted of felony drug abuse charges.

It's interesting that the knowledge of the abuse potential is not limited only to the pharmacists and physicians in the health care industry. During a one-year time period in 1993-94, a registered nurse who worked in an industrial first aid room for a large corporation in Ohio started ordering Carisoprodol and another non-schedule drug and proceeded to steal these two drugs. During this 12-month time period, she was able to order and steal approximately 2,500 dosage units of Carisoprodol.

In another case, a medical technician working in a physician's office started stealing prescription blanks from the physician's office. And during a 418-day time period, she forged prescriptions covering for a total of 9,920 doses of Carisoprodol.

She was also forging prescriptions for hydrocodone and APAP with codeine. These, the hydrocodone and the APAP with codeine, doses totalled about 6,000 dosage units. So her main drug of choice was the Carisoprodol.

The Board of Pharmacy has received documentation from various other law enforcement agencies as to the diversion of this drug. One of the handouts that you have today is from the Cincinnati

Police Department Pharmaceutical Diversion Unit.

This unit was formed in October of 1990. Through the end of 1996, this unit has documented the diversion of 25,237 dosage units of Carisoprodol. This ranks 11th in the listing of drugs in quantity since October of 1990. And almost every year, this drug falls either 10th or 11th on their list.

I think it's interesting in the letter that Sergeant Burke wrote to me that's part of the handout that they see Carisoprodol continuously as a widely abused pharmaceutical drug in Cincinnati with the steady street cost of three to four dollars per tablet in the street. And this is true across the State of Ohio. It ranges between three to five dollars on the streets.

He further points out that being over 25,000 dosage units as being diverted, that this has surpassed the amount of diversion that they have documented for drugs like Xanax and Ritalin. And it has similar street values to Valium, Darvocet, Xanax, and Tylenol with codeine, all controlled substances.

Another handout you have is a letter from a task force in southeastern Ohio. It covers an eight-county area. It's a very rural area. One of the counties they cover has no physicians and one

pharmacy in the county. They currently have 15 active cases involving Carisoprodol in those eight counties. These cases also involve narcotics and benzodiazepines.

In the discussions that we've had with crime labs and treatment programs around the state, they also have identified Carisoprodol as a substance abused, both from the analysis of tablets submitted to the crime labs and from the intake from known abusers to the treatment centers. And there is a letter in there. The top of it says, "Soma." It is from a Dr. Tarr, who is head of a treatment program in the Akron area.

In conclusion, I would like to state that the Ohio Chapter of NADDI, which is the National Association of Drug Diversion Investigators, which currently has approximately 80 members, fully recognizes that Carisoprodol is a drug that is routinely diverted into the illegal channels for abuse purposes.

Thank you very much.

CHAIRMAN SCHNEIDER: Thank you. Questions?

MS. FALKOWSKI: Yes. You mentioned 65 cases since 1987. Do you have a breakdown of the

frequency of that by each year so we can --

MR. BENEDICT: Yes. There's a handout.

MS. FALKOWSKI: Which one is that? Is it the one with all of the spreadsheets? Is it this one?

MR. BENEDICT: Yes.

MS. FALKOWSKI: Okay.

MR. BENEDICT: That's from the Board of Pharmacy. I'm sorry if it doesn't identify it.

MS. FALKOWSKI: Okay. Thank you.

CHAIRMAN SCHNEIDER: Doctor? Dr. Klein?

DR. KLEIN: Is the drug controlled in Ohio?

MR. BENEDICT: No, it is not at the current time.

DR. KLEIN: What procedures are available to the State of Ohio for controlling the drug?

MR. BENEDICT: For controlling it? It can go one of three ways. The federal government can control it, and it has an automatic passthrough in the state statutes. The legislature can pass it by law. And the Board of Pharmacy can put it into a controlled substance.

DR. KLEIN: Okay.

CHAIRMAN SCHNEIDER: Dr. Wright?

DR. WRIGHT: Since this is not currently

scheduled, if you find cases involving this prescription or diversion from a pharmacy or failure to have legitimate patient at the other end, what can you currently do about it? What action can you take?

MR. BENEDICT: I won't speak for the other states, but I will say Ohio is very lucky, as far as I'm concerned, in their laws in that the illegal sale or the forging of prescriptions for any prescription drug is a felony in the State of Ohio. So they are treated as felonies in Ohio currently.

DR. WRIGHT: So if these are reported to you, you can prosecute these as felonies right off the git-go?

MR. BENEDICT: Yes.

CHAIRMAN SCHNEIDER: Dr. Young?

DR. YOUNG: Has the State Board of Pharmacy taken action to take that third step for this compound?

MR. BENEDICT: Two years ago our board requested us to start gathering information to review this, which we are still in the process of doing, trying to get enough information.

DR. YOUNG: And when is the review scheduled?

MR. BENEDICT: Pardon me?

DR. YOUNG: When is the due date or the date --

MR. BENEDICT: There is no due date. We're gathering information. We're trying to see. Quite honestly, before I came with the Board of Pharmacy in 1978 the board tried to reschedule pentazocine into a Schedule II.

It went all the way to the Supreme Court. I was not part of the board at that point in time, but it's my understanding the Supreme Court said: You do not have enough evidence. And that was the end of it, did not give us the guideline as to what would be enough evidence.

So we are moving very carefully on this one --

DR. YOUNG: Thank you.

MR. BENEDICT: -- as well as a few other drugs.

CHAIRMAN SCHNEIDER: Ms. Falkowski?

MS. FALKOWSKI: I noticed that in your neighbor state of Kentucky, it's a Schedule IV. And I'm wondering when that happened and to what extent you think the scheduling of it in Kentucky may have contributed to some activities moving across the state line into your state.

MR. BENEDICT: It could have an impact in Cincinnati since Kentucky borders Cincinnati. As far as the rest of the state, I would say it would have no impact.

MS. FALKOWSKI: What year was that that it became --

MR. BENEDICT: I'm not aware of what year it was.

CHAIRMAN SCHNEIDER: Mr. Lloyd?

MR. LLOYD: I'm interested in the accountability and the inventory requirements for a non-controlled substance in Ohio and how that affects your reporting.

MR. BENEDICT: Ohio law requires that any prescription drug has to be accounted for for a period of three years, starting from the time it hits your pharmacy until the time it leaves. Naturally, there are much more stringent requirements for Schedule II substances, but the recordkeeping and type reports are pretty much the same.

In fact, in our role for reporting theft and diversion, it now covers not only controlled substances, but it covers dangerous drugs, period.

MR. LLOYD: Thank you.

DR. de WIT: I find it a little bit

difficult to evaluate these case reports in individual instances without relating it to the data for other drugs. I wonder if you can kind of at some point put this into perspective relative to other prescription drugs and other schedule drugs to give us an idea.

MR. BENEDICT: Since most of our work deals with health care professionals and the diversion and the theft of it, by far the hydrocodone products take up the bulk of the market for what we see is diverted and stolen as well as abused.

Because we deal with physicians and nurses also, I would say this is probably in our top 20 drugs, but because we don't work the street people that much, usually we are into addition or straight trafficking cases, which usually involves the controlled substances.

We still do have a major problem with amphetamine-type substances in the State of Ohio. So when you look at a dose-by-dose situation, when we get into a physician who is illegally distributing amphetamine substances, amphetamine-type substances, usually the IIIs and the IVs, the quantities are very significant, which would lower the percentage of this. But we still consider this a very serious problem.

CHAIRMAN SCHNEIDER: Dr. Wright?

DR. WRIGHT: If this was federally scheduled and passed through to your state, what effect would it have? What benefit would it have for you in your control efforts?

MR. BENEDICT: I think the main benefit it would have right now -- well, there's a couple. Right now there are approximately seven or eight pharmaceutical diversion units within drug task forces. That is going to increase to probably every drug task force in this state.

Ohio does have a three-filing system, where Schedule IIs are kept in a separate file, IIIs, IVs, and Vs are in a separate file, and prescription drugs, non-controlled, are in another file.

We went to this simply because about seven or eight years ago we started seeing the majority of our diversion in the IIIs, IVs, and Vs, rather than in the IIs. And it was a very time-consuming, painstaking operation to go through files looking for the controlled substances, even with the red "C" stamped on them.

So putting these prescriptions into the Schedule III, IV, and V file will benefit law enforcement. I think it will also bring to light a little bit better to the pharmacists' attention what's

going on.

There are a lot of wholesalers now that are reporting Carisoprodol sales as excessive purchases to both the DEA and to the Boards of Pharmacies, but this will mandate that everyone do it, not just have it done on a voluntary basis. So we will be better able to track the distribution of this drug.

Right now it is very difficult. I won't say it's very difficult because the wholesalers and the manufacturers do cooperate well, but when you make requests for sales of these products that are not controlled substances, it's a different animal for them to get that report together, rather than when you're asking for a controlled substance report. So I think it would bring to light the problem a lot more.

I can tell you right now it's not uncommon at all when drug task forces kick in doors of crack cocaine houses. Pharmaceuticals are almost always found in some fashion. Benzodiazepines and Carisoprodol seem to be the two most found drugs in these crack houses.

CHAIRMAN SCHNEIDER: Any other questions?

(No response.)

**CHAIRMAN SCHNEIDER: Thank you very much, Mr. Benedict.**

**MR. BENEDICT: Thank you.**

**OPEN PUBLIC SESSION**

**CHAIRMAN SCHNEIDER: We will open the program to the public. For those who wish to speak, please, again, I remind you to use a microphone. I wanted to stay on schedule, but I didn't think it would be this good.**

**Then I will close the open public session. I think it's a little early for a break. So our next presentation will be the sponsor's presentation if they are prepared to start at this time. And if each of you would please introduce yourselves, I'd be most grateful.**

**DR. COSTIN: Thank you very much, Mr. Chairman.**

**SPONSOR PRESENTATION**

**DR. COSTIN: I am Dr. James Costin. I am Vice President for Research and Development for Wallace Laboratories at Carter-Wallace. We are certainly very happy to be here this morning, Mr. Chairman. I am especially happy to be here since I almost went to the wrong Holiday Inn on Rockville Pile, but we're, nevertheless, very happy to be here.**

We appreciate your including us as a sponsor for our remarks this morning.

We're very happy to participate in this conference this morning, the Committee's meeting, especially since we would like to address some issues that we feel you need to consider in your deliberations as they go forward in this meeting as well as additional future meetings in determining whether or not there is a sufficient body of evidence, scientific or otherwise, to recommend scheduling. So we appreciate the opportunity to make these comments.

Our presentation this morning, which has changed a little bit during the last 12 hours, will by necessity focus on the FDA's perspective and on the data analysis provided by the DEA document. Although we did receive the FDA's document in a very timely fashion as usual, our copy did not include the DEA's Eight Factor Analysis behind your Tab A-1, I think.

Although we have requested this document through multiple sources multiple times, we have not had access to this document until it was finally provided to us late yesterday afternoon, literally delivered to my hotel while I was waiting for this meeting.

This very detailed, obviously very

laboriously prepared document by the FDA is obviously an extremely important document for this Committee and all of us to consider.

We have had no chance at all to review this document in any depth, but we think that our comments and our perhaps different interpretations of the data presented in that document deserve consideration by this Committee at some time in the future.

Conclusions in the DEA document at first glance appear to rest strongly on a major premise that Carisoprodol is a pro-drug that is metabolized to meprobamate, a premise which has no valid scientific basis and to which we want the opportunity to comment in depth and with our expert consultants as well.

As I will mention a bit later, Carter-Wallace has an ongoing human pharmacokinetic metabolism study which will provide scientifically valid data on the amount of Carisoprodol that may be metabolized to meprobamate utilizing proper, current, modern analytical methods and an appropriately designed clinical study. Indeed, we had requested a short postponement of this Advisory Committee until this data was available, but this request was denied at the time.

Accordingly, since we believe that it is extremely important, scientifically important, and very proper for the Committee to consider what will be Carter-Wallace's and our consultants' rather extensive comments on the DEA analysis as well as the results of the ongoing human study, we would like to be able to present these comments to this Committee, to the FDA at some time in the future prior to any recommendation for scheduling.

With that brief introduction, I'll go ahead with my comments that I had prepared. I would like to reflect to the Committee if you don't know it -- I'm not sure that I knew it until I came to Carter-Wallace -- Carter-Wallace was the originator of Carisoprodol.

It has been manufactured and was introduced by Carter-Wallace in 1959 as Soma. This was followed in 1960 by an introduction of Soma compound, which, as most of you may know, is a Soma-containing aspirin.

Since that time, a very large volume, 5.2 billion tablets, have been dispensed in approximately 120 million prescriptions. This results in a very large, 4.2 million, patient year experience with this drug.

As I said, Carter-Wallace's understanding of this meeting is that it will examine the existing scientific data to determine if there's any scientific basis to conclude that Carisoprodol is or reasonably has the potential to be an addictive substance. And we're very happy to try to provide information that we have as well as accumulate additional information on this subject.

We're prepared to respond to information currently available and for the most part supplied to the Committee by the FDA document. We are also prepared to respond to available information concerning the incidence of dependency, adverse drug reports, and how these are profiled against the increasing prescriptions for Carisoprodol.

I think that the comments that I would like to offer at this point are really basically in five general areas. These basically also parallel our document that we sent to the Committee; first of all, a few comments on the metabolism of Carisoprodol per se.

We acknowledge the publication supplied to the Committee by the FDA in their document, specifically behind Tab B. And we would like to note some of the following comments.

First of all, the animal studies have demonstrated a low percentage of Carisoprodol is actually metabolized to active meprobamate. This is exampled in your handout by the Douglas study.

The Olsen study, also in your handout, suggests that a higher level of Carisoprodol may be metabolized to meprobamate, but, and I think but very importantly and very appropriately, acknowledges that the proper analytical methodologies were not used to determine the difference between Carisoprodol, meprobamate, and their known inactive metabolites.

Indeed, if you look at the clinical side of that equation, in human studies in which patients are maintained on high doses of Carisoprodol for an extended period of time and then the Carisoprodol is abruptly withdrawn, there are no withdrawal signs. If meprobamate is indeed a significant metabolite, strong withdrawal signs should have been seen, as they are when patients are abruptly withdrawn from meprobamate, for example.

Since the issue of the amount of Carisoprodol that may be metabolized to meprobamate in humans is very central to the issues under consideration today, Carter-Wallace commissioned a study which is currently underway. And this study

will definitively resolve the question using mass spectrometric techniques. This data should be available to us sometime next month, in March.

A second area I'd like to address some comments to is comparative pharmacology of Carisoprodol and meprobamate. In our document that we supplied to the Committee, a table of information included physical, chemical, neurophysiological, and toxicological data, which shows significant differences between Carisoprodol and meprobamate and establishes that these two drugs are two clearly different entities, both chemically as well as *in vivo*.

In fact, if you look at the pharmacology of Carisoprodol, it more closely resembles that of other centrally acting muscle relaxants, such as methocarbamal, Robaxin, and mephenesin.

Some of the types of studies that I think would currently be used by this Committee and the FDA to evaluate a drug's addictive potential are clearly lacking for Carisoprodol. This drug has been marketed for over 40 years, and there has never been any reason to pursue such studies given that the ADR profile and the scientific profile of this drug did not warrant it.

Nevertheless, Carter-Wallace is certainly willing to consider carrying out evaluations, such as self-administration studies, drug discrimination studies, with a submission to the College on Drug Dependency's stimulant and depressant evaluation program should this Committee and the FDA conclude that this type of data would be needed and would be valuable in evaluating the addictive potential for Carisoprodol.

A word about the increased use of Carisoprodol, which has been mentioned several times and apparently is also mentioned quite extensively in the DEA document.

The FDA document that we were able to review presented the data for both brand and generic Carisoprodol. We find ourselves in virtual agreement with the figures presented in that.

Over the last approximately ten years, the total oral muscle relaxant usage has increased with rates of around one to five percent annually. Over this same time period, the brand plus generic Carisoprodol 350-milligram prescriptions have grown by approximately 15 percent per year.

Now, there are very common market forces that become evident if you plot these out which

explain the larger growth rates and increased market share of Carisoprodol, such things as the active promotion of Soma by Carter-Wallace, the discontinuation of promotion by some major competitors, stricter control of benzodiazepines, changes in the prescription-tracking procedures from market research firms that all of us use to get an estimate of the size of use.

The changes in the adverse drug report profiles for Carisoprodol, particularly in relationship to the prescriptions, also deserve a couple of comments, we believe.

The FDA documents indicate that 421 adverse drug reports for Carisoprodol, 350 milligrams, were reported over a 27-year period. Total brand plus generic prescriptions for Carisoprodol for this same time period were approximately 57 and a half million prescriptions. FDA documents also indicate 31 of these reports were dependency reports and that 15 of these occurred during the last 5 years.

Now, I would submit to anyone that 421 total adverse drug reports over a 27-year period with 57 million-plus prescriptions is rare by any standard you want to apply and certainly by published FDA standards.

The 31 dependency reports are ever rarer, especially when these show no sequential increase from year to year and could justifiably be postulated to have occurred, at least in part or in whole, as a result of the implementation of better tracking or reporting systems during this time.

I think someone had mentioned a little bit earlier today that a resolution or a reconciliation of different databases if they're telling us different things is an opportunity for us to consider as we move forward.

Certainly the increased reporting and trafficking being reported from other databases do not really comport with the changes seen in the ADR reports. The ADR reports as they relate to increasing prescription size are of interest if you look at those on an annual basis as well.

When you look at either the total, 421, or the dependency, 31, adverse drug reports and you relate these to the number of prescriptions during those periods, the ratio decreases, not increases with the exception of one aberrant year out of 35. And this aberrant year was primarily on the basis of increased allergy reports during that time, not increased dependency reports.

In all of these years, however, if you take the data that was supplied to you, the incidence of dependency, ADRs, relative to prescriptions is an incidence of 0.00012 and is usually, almost invariably, associated with multiple drug misuse.

In summary, then, Mr. Chairman, I would just like to make a few small points. First of all, Carter-Wallace believes that the available scientific data do not support an addictive potential for Carisoprodol with its 38-year, 88, roughly 120 million-prescription history.

We believe that the increases in prescriptions and market share for Carisoprodol is very easily explained on very common market forces. The adverse drug reports have not increased proportionately to increasing prescriptions. They have actually decreased. The total number of adverse drug reports, and especially the dependency reports, are clearly classified as rare events.

Finally, I would just like to briefly, very briefly, emphasize two points that I made in my introductory comments. And that is since the studies that are relied upon in the DEA report are basically that Carisoprodol is a pro drug for meprobamate and these are acknowledged by the studies on authors to be

inadequate for coming to this determination and since the DEA document operates and depends upon this premise, this in our opinion invalidated premise, Carter-Wallace believes that the results of the ongoing study are very important for this Committee to consider.

However, I think even more critical is our being allowed to properly review this DEA analysis, obtain some expert consultants' comments on this very important document, and provide these to the Committee so that a balanced assessment of this information can be made.

We are very happy, Mr. Chairman, once again, to participate in this meeting this morning. We look forward to trying to work with the agency, with this Committee in collecting any additional data that you think would be valuable in this as well as coming up with any type of ways that we can help monitor the situation for you. We thank you for this opportunity to participate.

CHAIRMAN SCHNEIDER: Thank you very much.

Ms. Cohen?

MS. COHEN: Yes. Of these 421 individuals who had adverse drug reports -- and I might add for the person who has had the adverse drug problems, it

means a lot to them; it might not seem like a big number, but it still affects them -- and the 31 dependency reports, did you interview these people, talk to them to find out exactly what it was all about?

DR. COSTIN: Most of the adverse drug reports are obviously reports handled through old 1639s or MEDWATCH forms or something that came into the FDA database. To the extent that they came to us and we reported them, then we have information, as much as you can get, from those reports.

Some of the reports obviously did not come to us. Some of them are generic reports. And that would be contained in the FDA database. And that's available through FOIA.

MS. COHEN: Well, in the real world, consumers don't always report what happens to them. So if you got this number, you can be sure there are many others who have not reported the --

DR. COSTIN: I think you're absolutely right. I think we're all very aware, acutely aware, of the under-reporting of all databases of this sort. I think since health professionals are involved and to the extent that the former speaker certainly indicated that much of the focus is involved with health

professionals, to the extent that these are becoming increasingly problematic for these people, one would have expected a larger increase in the ADR reports.

MS. COHEN: And my other question is: -- and it was answered before in terms of the wholesalers and the company itself -- Have you taken any steps and measures to identify those distributors who are requesting much more drug than before?

And also in the company, do you go through your statistics and say, "Well, this looks a little unusual. I wonder what the trend is. Why is this happening?" Has there been such an analysis within the company?

DR. COSTIN: Yes, ma'am, from one standpoint, certainly. And that is that we obviously track prescription rates, sales, if you please, basically so we can decide how much to manufacture.

You have to realize, obviously, that Soma per se represents a minority of the market. The majority of the market is represented by generics. And what our information and then once we went back and looked at all the information supplied for generics and other information, it's obvious that the increasing utilization of this compound was responding to market forces.

This is a very promotionally responsive market. If you see when we started promotion, it increased. If you see when competitors backed off of their promotion, the share, market share, increased. So we think we have an explanation for it.

On the other hand --

MS. COHEN: That might be wishful thinking.

DR. COSTIN: Well, no. I will acknowledge to you that to the extent that this type of information can be used or an analysis of this, this would by necessity involve the cooperation of generic companies, brand name companies.

And there has been a very innovative approach to that certainly with another drug. We are aware of that. And to the extent that we could enlist the cooperation of others, it's something that's certainly worth considering. It has been put on the table, and I think it's something worthy of consideration.

MS. COHEN: Thank you.

DR. COSTIN: But it would have to involve a lot of companies.

CHAIRMAN SCHNEIDER: Ms. Falkowski?

MS. FALKOWSKI: Where is Soma

manufactured?

DR. COSTIN: Where is it manufactured?

MS. FALKOWSKI: Yes, yes.

DR. COSTIN: You mean literally manufactured?

MS. FALKOWSKI: Yes.

DR. COSTIN: At Carter-Wallace in --

MS. FALKOWSKI: Are they all in this country or are they in other countries?

DR. COSTIN: No. In this country.

MS. FALKOWSKI: All right. Is it known in any other countries by different names other than Soma?

DR. COSTIN: I'm sure it is. I can't tell you what it is. I'm sure it is. I think that -- I'm sorry?

CHAIRMAN SCHNEIDER: It's in the literature, the handout here.

MS. FALKOWSKI: Okay.

CHAIRMAN SCHNEIDER: If not, I happen to have one which was of my own research. Let me answer that question for you if I can. It comes under the name of -- well, all right. Let' go to your own handout, Page 35.

Dr. Young?

DR. YOUNG: No. That was it.

CHAIRMAN SCHNEIDER: That was it? Dr. Khuri?

DR. KHURI: You had mentioned that competitors had backed off from this product. What were some of the reasons?

DR. COSTIN: No. Competitor products had backed off.

DR. KHURI: Products.

DR. COSTIN: In other words, if you have total market share for all muscle relaxants and Carisoprodol -- I'll make up some figures -- happens to have ten percent of that market and another drug happens to have ten percent, if they back off of their promotion in this very promotional responsive market, if their market share drops five percent, you may well expect others to pick up the five percent.

DR. KHURI: Why? My question was: Why did they back off the promotion?

DR. COSTIN: The reason that this particular company and this particular drug are one major example is that it went off patent. It was market forces, pure and simple.

DR. KHURI: Thank you.

DR. STRAIN: For Soma, does the label

indicate it's to be used only for a time-limited period or is it proper for patients to use it chronically?

DR. COSTIN: I'm sorry. I didn't hear the last part.

DR. STRAIN: Does the label recommendation suggest a time-limited period of use or does it recommend chronic use or hold open the potential for chronic use?

DR. COSTIN: No, I don't think it holds open the potential. As a matter of fact, the labeling indications for Soma are as an adjunct, as an adjunct. And, if you'd like, I'll read you the indications specifically.

It is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. The usual adult dose is blah blah blah.

Clearly it's targeted for the acute condition and as an adjunct to physical therapy and other things that a physician would have to consider.

DR. STRAIN: Is there any indication based on sales or -- I'm thinking of the analogy to benzodiazepines used as hypnotics, which are

recommended for only acute use as well. But a large percentage of benzodiazepine prescriptions actually are given for chronic usage, even though that is not what the indication is.

And I'm wondering if there's any evidence of a similar database regarding Soma that might indicate whether there are patients using it on a chronic basis, rather than an acute basis. Do you have any --

DR. COSTIN: I'm certain that you could try to tease that type of information out of prescription databases in terms of refills, as opposed to new 'scripts, et cetera, et cetera.

I don't have that information right now in hand, but I suspect that that data could be developed. The new 'scripts -- well, I don't have that data right now, but I suspect it could be developed.

CHAIRMAN SCHNEIDER: The Chair would like to ask a couple of questions. I want to be sure I heard what you said correctly that you have studies that show no withdrawal symptomatology from the use of this drug. Am I hearing accurately?

DR. COSTIN: The statement that I made I think was that when you -- are you talking about the Carisoprodol used over an extended period of time and

then was abruptly withdrawn?

CHAIRMAN SCHNEIDER: Yes, sir.

DR. COSTIN: Then there were no withdrawal symptoms or signs. Yes, that's a statement that we made.

CHAIRMAN SCHNEIDER: Is that based on a study or case reports?

DR. COSTIN: That is based on study information. I'll be happy to allow one of our experts to comment on it if you like, Dr. Harris, Dr. Lou Harris.

CHAIRMAN SCHNEIDER: Yes, I'd appreciate that.

DR. HARRIS: To the best of my knowledge --

CHAIRMAN SCHNEIDER: Your name, sir, is?

DR. HARRIS: My name is Lou Harris. I'm Professor of Pharmacology at the Medical College of Virginia, Virginia Commonwealth University. And I'm a consultant to Carter-Wallace on this particular issue.

There have been, to my knowledge, two reasonable studies carried out, one in dog by Deneau and his colleagues at the University of Michigan, where they did first a substitution study in

barbiturate-dependent dogs and found that Carisoprodol partially substituted for the barbiturate.

The second was a primary physical dependence studies, where the dogs would contain Carisoprodol for a significant period of time, then abruptly were withdrawn. And there was very little indication of withdrawal signs.

The second study is a study in man carried out at the Addiction Research Center at Lexington. You have to put these things in context. We're back now in the early 1960s. It was well before many of the more finer methods of assessing abuse potential were available to us.

In the Lexington study, first of all, the drug was study in morphine-dependent subjects, who were put into withdrawal. Substitution studies were done. The drug did not substitute for morphine in those studies.

The second part of that study was a subjective effect study, where the drug was given at various doses and in a blind condition. Subjects were asked to identify the drug. And signs and symptoms were noted. Signs and symptoms were not opiate-like. They were not barbiturate-like. But they were something in between.

Finally, I believe it was four or five subjects were chronically medicated, three or four for a period of a week or two with doses -- and, again, there are documents, papers, available to all of you -- and then abruptly withdrawn for very little indication of withdrawal signs.

One person was maintained at very high doses for 60 days and then abruptly withdrawn or substituted with placebo. His report was that he couldn't distinguish with the placebo and the drug. There were no withdrawal signs. He couldn't tell when he had received the placebo.

Again, these are old studies. And, certainly, my advice is that we should be looking -- if there's need to do so, we should be looking at some more modern methods.

Therefore, the data so far that we have from both animals and man; that is, actual studies that were carried out, not anecdotal or case reports, doesn't produce much in the way of physical dependence.

CHAIRMAN SCHNEIDER: Thank you.

Any questions of Dr. Harris? Yes, Dr. Khuri?

DR. KHURI: Since some of the argument, of

course, has been based on the similarity to and the metabolism to meprobamate, which is in question, I fully understand, what is our present knowledge about meprobamate abuse as compared with other drugs of abuse from the DEA perspective?

There is a literature I know in the eight-fold analysis, but it's based on 1977, earlier literature.

DR. COSTIN: I believe that part of the FDA presentation included some meprobamate analysis, didn't it?

DR. WRIGHT: We'll have some additional data on that.

DR. KHURI: Thank you. Thank you.

DR. COSTIN: Yes. Maybe I should hold and let him comment on that. From our perspective, though, I will comment on it. Our reports, is that what you're referring to?

DR. KHURI: Yes.

DR. COSTIN: Our reports have been absolutely flat on sales.

DR. KHURI: I just wanted that repeated. Thanks.

CHAIRMAN SCHNEIDER: Dr. Wright?

DR. WRIGHT: I have two questions. One is

a '90s kind of question. We have become aware of late that there is quite a -- I don't know how large but certainly very active -- users' group on the internet exploring various pharmaceuticals and describing their subjective effects and promoting or extolling the virtues of various companies' products for abuse purposes.

Have you looked on the internet for mentions of this drug or have you looked in press reports or done any form of surveillance in preparation for this meeting?

DR. COSTIN: Not in terms of preparation for this meeting. We do actively scan various sources within the 'net with personnel within R&D. And it's primarily for the purpose of picking up any type of mentions in the lay or in the professional press relative to Carisoprodol.

Most of these revolve around various state activities. Some of them involve the mention of physicians or pharmacists being arrested, and this was part of a drug cache that was picked up.

So we do monitor that. We are aware of that. We have not done any formal collection or analysis. And we have certainly not quantified the information on internet.

Dr. Flanagan here is in charge of a medical department. Do you have any additional comments, Harry?

CHAIRMAN SCHNEIDER: Identify yourself, please, sir.

DR. FLANAGAN: Dr. Harry Flanagan, Wallace Medical Department.

Again, we receive these reports. And mostly we receive them in the form of printout. And we document them. But, again, as Dr. Costin has mentioned, we haven't quantified them to any degree.

We also search the medical literature on a monthly basis for all Carisoprodol reports that appear in the medical literature either as case reports, which is what the primary type of reporting is.

So we do monitor it monthly like that, but we have not done anything formally on internet.

DR. COSTIN: This is primarily -- I'm sorry.

DR. WRIGHT: Before you step down, so you have been reading these for some time?

DR. FLANAGAN: We collect the medical -- the reports that we have that are identified, yes. Again, I personally am not aware of reading any

particular lay type of information.

DR. WRIGHT: Okay. Do you have a --

DR. COSTIN: Yes. Our purpose in doing this is primarily to scan the information that's out there relative to any possible adverse type of drug reaction that is being reported for any of our products. We do this with all of our products.

As a matter of fact, if I'm not mistaken, when it came to our attention that reports of Carisoprodol misuse were coming up, I believe we even hounded the chairman of this Committee for a while for some reports. So we're doing this primarily from the standpoint of carrying out our charge to report adverse drug reactions to the FDA. That's our primary purpose in doing it.

CHAIRMAN SCHNEIDER: I'd like to ask another question. Yes, I have been hounded, but I have not avoided it.

DR. COSTIN: No, you haven't. You've responded very well.

CHAIRMAN SCHNEIDER: As a matter of fact, you have made me lose a few days of other activity because of your hounding.

When diazepam, Valium, breaks down, it breaks down into at least one, if not two, other

psychoactive products. When this drug breaks down, it breaks down into meprobamate, which is a psychoactive product. However, the primary drug is also psychoactive apparently. Is it related to the meprobamate?

My question really is to although your stand is that the breakdown of this drug -- you know, I have to stop here. I have heard multiple pronunciations of this drug. Would you please educate me as to the correct pronunciation of it?

I see there are variances of opinion in your group over here.

DR. COSTIN: I'm disadvantaged, though, because any pronunciation I give is going to have a Southern accent to it. So I'm automatically suspect in a drug which was developed in northern territories. So I call it Carisoprodol.

CHAIRMAN SCHNEIDER: All right. Carisoprodol. I'm from southern California. I guess I don't talk with a Southern accent, though.

The Carisoprodol per se appears to be a psychoactive drug. Your premise is -- and maybe I'm hearing that the premise of the FDA or the DEA is that the breakdown product is the total culprit here. I'd like your comment, sir, on the psychoactivity of

Carisoprodol per se.

DR. COSTIN: Carisoprodol per se.

CHAIRMAN SCHNEIDER: Yes.

DR. COSTIN: Well, first of all, I think that I agree with you. But having not reviewed the DEA document, I can't comment much further than that. But I think a lot of the premise is that it is a pro drug.

And if that's the case and that's the reason for bringing the meprobamate information into that document, then I would presume that the distinction or the correlation is trying to be drawn to it that meprobamate is a major player.

However, in terms of the psychoactivity of the Carisoprodol per se, Carisoprodol along with several other carbamates back in the '50s were being developed by Carter-Wallace.

And the primary reason for this development program, as you're probably very well-aware, is the development of the tranquilizers. And meprobamate was certainly one of the first, was the first, tranquilizer out there.

Indeed, Carisoprodol was looked at during this time. It was looked at specifically for tranquilizing effect. And it was shelved because it

didn't have any tranquilizing effect to warrant the development program that Carter-Wallace was pursuing at the time, namely they wanted something that had significant, profound, if you please, tranquilizing effects.

Carisoprodol clearly didn't have this in the studies.

CHAIRMAN SCHNEIDER: Didn't have it at all or didn't have it in amounts strong enough to warrant its competition with the others?

DR. COSTIN: Virtually none. I mean, you certainly would not use this drug to even remotely think of trying to go with an NDA for development of this. I mean, it's just nonexistent.

CHAIRMAN SCHNEIDER: So "none" is not the word? "Not enough" would be the word?

DR. COSTIN: I think "none" is an appropriate word. I think it's a very appropriate word.

Dr. Steiner, who's here, might wish to comment on that.

DR. STEINER: My name is Solomon Steiner, and I'm a consultant to Carter-Wallace on this matter, Professor Emeritus of Neuroscience at City University of New York, NYU School of Medicine.

I think first one should distinguish between psychoactive and affecting the central nervous system. Carisoprodol does affect the central nervous system. It's a centrally acting muscle relaxant. And it works particularly in reticular formation.

It is devoid of a number of and particularly, interestingly, devoid because of its chemical relationship or similarity to meprobamate. That's what makes it particularly interesting, that it is devoid in animal studies of a variety of effects that one typically sees with the meprobamate and with Valium, with benzodiazepines. And it is particularly devoid of it.

It's not that it has not enough of it and that somehow if we could make more of it, it would be better. It doesn't happen. And that's what makes it interesting.

It's also interesting because if you really believe that Carisoprodol is being metabolized to meprobamate, you would expect that either animals or humans maintained on Carisoprodol for any extended period of time would show responses that you see to meprobamatel. And you don't see it with Carisoprodol, which casts real question as to how much, if any, of Carisoprodol is being metabolized to meprobamate and

functioning in that respect.

Withdrawal is one effect that one can point to. You just don't see withdrawal with Carisoprodol. You do with meprobamate. So when you maintain someone on Carisoprodol, why don't you see abrupt withdrawal symptoms when you withdraw them if it's being metabolized to meprobamate? And that's basically the point.

So I would say that it would be fair to say that Carisoprodol is a CNS-active drug in that it's working on the reticular formation primarily as a muscle relaxant, but it would not be accurate to say that it's a psychoactive drug in terms that it has its primary effect on behavior.

CHAIRMAN SCHNEIDER: Dr. Wright?

DR. WRIGHT: Before you leave, sir, so based on the animal data and the human data so far, you believe that there is little evidence for a human withdrawal system?

DR. STEINER: Yes, sir.

DR. WRIGHT: So that could be studied at the clinic?

DR. STEINER: That certainly could be studied at the clinic, yes.

DR. WRIGHT: Thank you.

**CHAIRMAN SCHNEIDER: Before I turn it over to someone else, let me change our terminology between you and me. You have stimulated me. You have not hounded me because I have had personal experience and my staff has had personal experience to the contrary. And this has not been documented.**

**And so I must tell the Committee that we will go back to the record room and go back to our documentation and try and provide you with some accurate documentation which does not totally agree with the evidence that has been presented today.**

**Ms. Cohen?**

**MS. COHEN: No. Dr. Khuri. I'll let her go first.**

**CHAIRMAN SCHNEIDER: Dr. Khuri?**

**DR. KHURI: No. I just wanted to add another question for the last speaker for a moment. You have established certain important points for me, but I wondered about the potentiation of euphorigenic aspects of other drugs of abuse, granted that Carisoprodol does not have a withdrawal, clearly defined withdrawal, syndrome. But what about potentiation of euphorigenic effects of other drugs: opiates and tranquilizers?**

**DR. HARRIS: I think that's a possibility.**

It's just never been studied in any real fashion. Experimental methods now exist to test that hypothesis, both in animals and man. I don't think there's evidence for or against that possibility.

I do think that some of the prescribing habits that you've heard about of physicians, if you have -- and I'm not a physician. I must beg off. But I do teach pharmacology.

A physician faced with muscle pain, particularly back pain, is often faced with very difficult situations. They often tend to use combinations of analgesic-type muscle relaxants combined with nonsteroidal anti-inflammatory agents, and if they are not getting relief when they get to that point adding usually an opiate of one type.

And that's why there are combination products, as you saw, galore with this drug and also with other drugs that fit into this case. Mephenesin, which I don't believe is available anymore, was very heavily used in that regard. Methocarbamal is another example of a drug in this class that exists as combination products.

But, again, I don't think that it's been studied adequately. And I think that it's an interesting point. I don't know how much this adds to

the purported misuse or abuse of the drug.

DR. KHURI: Well, it wouldn't come so much from therapeutic use. I use the term "euphorigenic" advisedly. It would come from street --

DR. HARRIS: Yes. Well, that's what I'm saying. What you're seeing in a lot of the reports is its combined use with opiates is not being used in my opinion based on its pharmacology to produce opiate-like effects that would help these but maybe its effects combined with the opiate effects. You can say that about practically any psychoactive drug.

I would not say this is not a psychoactive drug. This drug affects the central nervous system, psychic, whatever. It's different from meprobamate. It's different from a barbiturate. It's different from an opiate. But it does produce effects on the central nervous system.

Now, if you want to try to distinguish between central effects and psychoactive, define psychoactive for me.

DR. STEINER: Okay. I will.

DR. HARRIS: Please I'm sorry. You've got to see that this is not a clear-cut and dry issue here.

CHAIRMAN SCHNEIDER: Go ahead.

DR. STEINER: I agree that little is known, but I should point out that, first of all, I would make a distinction -- I think it's a useful distinction -- to talk about a drug that affects the central nervous system: on the one hand, because there are lots of effects on the central nervous system --

CHAIRMAN SCHNEIDER: I don't want a long lecture here, sir. I want --

DR. STEINER: I'll try to keep it brief.

-- and, secondly, alternatively, drugs whose primary effect is to alter behavior. And that's what I consider a psychoactive drug to be. An anticonvulsant is not a psychoactive drug in my lexicon, but it certainly affects the activity of the central nervous system. A centrally acting muscle relaxant is not a psychoactive drug in my lexicon, but it certainly affects the central nervous system.

I want to make one other point. The fact that the lay community frequently abuses a drug is really no indication of the pharmacological properties. I'll give you one illustration, which many of you will remember, having some gray hairs.

In the '70s there was a great deal of smoking of banana skins based on a little bit of

knowledge that there's a lot of serotonin in banana skins. And people were smoking banana skins, kids were smoking banana skins, because they thought if they could increase their level of serotonin in the brain, they'd get a wonderful high. They just didn't know anything about the blood brain barrier.

So, while there is serotonin in banana skins, it doesn't get into the brain and really does not have any psychoactive effects other than a placebo effect, which is very powerful and which I should point out was the basis of medicine for most of human history.

Thank you.

CHAIRMAN SCHNEIDER: Thank you.

Dr. Young?

DR. YOUNG: I have a question that may be more appropriate for the DEA. Was the company ever asked to submit this compound through the DEA stimulant-sedative screen, the self-administration screen?

DR. COSTIN: No. When was the program introduced?

DR. HARRIS: It was introduced in the late '80s, but we have never had that submitted to us. I can't answer the question about whether the DEA

requested it to be submitted.

DR. YOUNG: So it didn't come through the --

DR. HARRIS: It has never come through the testing program.

DR. YOUNG: It's never come through the CPDD --

DR. HARRIS: Right.

DR. YOUNG: -- testing program?

DR. HARRIS: Right, right.

DR. YOUNG: Is there someone from the DEA that can say whether or not this compound was ever examined through its self-administration program? Was it ever requested?

CHAIRMAN SCHNEIDER: Use a microphone, please.

DR. HUTCHINSON: Not to my knowledge.

CHAIRMAN SCHNEIDER: Dr. Wright?

DR. WRIGHT: Yes. This is a difficult question. You may wish to defer your answer to this question. Parke-Davis established an oral chloramphenicol surveillance program when the drug was off patent to ensure that their company never had to bear the consequences of aplastic anemia related to either their product or to a generic one.

Is the marketing of this drug such that one could possibly work with the DEA or with state boards of pharmacy to try to identify misuse or misprescribing?

DR. COSTIN: I clearly think that opportunity is there. As I've indicated before, we as the brand manufacturer of this from a volume standpoint deal with a small part of the entire Carisoprodol market.

So I think if the DEA, FDA, Carter Wallace, and the generic companies could find a common ground there, I think the opportunity is there based upon the volume of it.

So I know what you're talking about. I understand what you're talking about. And I think that the opportunity is there. Whether or not one would be able to pull it off or not I think would depend upon a lot of cooperation between a lot of competing forces here or a lot of perhaps synergistic forces.

DR. WRIGHT: Then I'll follow up with a second question. Do you perceive it to be in the best interest of your firm to try to control this prescription of your product?

DR. COSTIN: Absolutely. We have

suggested, as a matter of fact, many times. We have no interest. It does nothing to a drug to have it misused. We end up with meetings like this with conflicting information. It does nothing more than to hurt any legitimate manufacturers.

And, as a consequence, I think we would be very interested in learning how to do this. We would certainly propose to various state agencies that if this is a problem and if you're having trouble controlling it on a misdemeanor level, then we're all for making it a felonious act to have this in your possession illegally.

So I think there are other remedies available to deal with this issue. The fact that we would like to promote the legitimate, legal use of the compound is a very sincere premise that we would have, no doubt about it.

CHAIRMAN SCHNEIDER: Unless there are other questions, I would thank you very much.

Dr. Klein?

DR. KLEIN: I would just like to clear up a small housekeeping issue. When we receive a Freedom of Information request, first of all, it's handled administratively by our Freedom of Information Office. And we release only documents that are the FDA's.

When the request includes documents that involve another agency, in this case involve the Drug Enforcement Administration, that has to be handled by the Freedom of Information Office within the Drug Enforcement Administration, not within the FDA.

DR. COSTIN: Right. My comments, my other comments, Dr. Klein, were not indicative of responsiveness on the FDA's part. FDA has always been very responsive.

We had pursued that request through other areas. And my only indication this morning was to try to indicate that this was the first time that I have ever been associated with any advisory committee -- I've been before quite a few -- to which the participants of the advisory committee, including the sponsor, had not been given access to a document which was sent to the full committee. I think that's an exception to which I know of no parallel.

That was my indication. I did not mean to, certainly, indicate the FDA was not responsive. You have been very responsive.

CHAIRMAN SCHNEIDER: So noted. We will adjourn for 15 minutes. The speakers scheduled for 1:00 o'clock have graciously come in early. So we will be able to go ahead at 11:00.

(Whereupon, the foregoing matter went off the record at 10:49 a.m. and went back on the record at 11:01 a.m.)

CHAIRMAN SCHNEIDER: I do appreciate very much the afternoon speakers coming in early. Some of us have a long way to travel. And if we can get out at an earlier time than originally scheduled, it would be very helpful to us and our families, who have to meet us at midnight at the airport in California.

So I think that the order of speaking will be, as I see it, Dr. Dale Conner will be first, then Dr. Raines, Dr. Staats, Dr, Kaplan, and Dr. Calderon. Is that agreeable with everybody? All right.

Then I'd like to introduce Dr. Dale Conner, a Pharm.D., a team leader, Office of Clinical Pharmacology and Biopharmaceuticals.

## FDA PRESENTATION

## PHARMACOKINETICS AND METABOLISM

DR. CONNER: I put the title of this particular very short talk as "Pharmacokinetics and Metabolism of Carisoprodol." Basically there's not a huge amount on this topic in the literature. It really boils down to one prospectively performed study and a lot of case reports or incidental reports about the alleged metabolism.

I'm going to spend my brief time pretty much talking about the article which you have been given in your packages and which has been alluded to before by the sponsor.

The particular question from my vantage point from certain of the questions that this Committee has been posed is: Is Carisoprodol metabolized to meprobamate? And, if so, to what extent?

I think most of the incidental information in the literature seems to imply that there is at least some metabolism to meprobamate. So if one accepts that, the question is: Is it important? Is it a large amount or a small amount? And under what conditions does it happen?

Next. And, of course, I mentioned the article that I'm going to kind of concentrate and go over briefly, which is the Olsen article, which I think you've all read or at least had a chance to look at, in "Therapeutic Drug Monitoring." That's a fairly recent report, 1994.

To just briefly go over the design of the study -- the sponsor has referred to a study which is currently ongoing. Their study, if I'm reading their summary of the study report, -- I haven't actually

seen an in-depth protocol -- seems to be a very similar type of approach to this with possibly a few improvements and certainly analytical analysis but basically has the same type of approach, roughly the same size of study.

In this study there were ten healthy subjects: six male and four female. And after an overnight fast, they received 700 milligrams, which was 2 tablets, of Carisoprodol by mouth in the morning.

Just because in the FDA we're always concentrating on this, this was, I believe, a European formulation of Carisoprodol, which I'm not really certain is available in this country.

The blood samples were as I stated here. So it was fairly intensively sampled out to 24 hours. And there was a single subject, whom I'll address later, who had additional samples drawn beyond that point out in time.

And this was assayed by gas chromatography, which the authors themselves in an honest self-criticism said that, although this is a good method, -- and I think they did a very good job as far as the analytical technique in assuring that what they were seeing and calling either meprobamate

or Carisoprodol was indeed that.

Technically speaking, it isn't an absolute identification, which I believe the sponsor in their upcoming study is actually using a GCMS method, which is a much more positive identification.

But usually this is the type of study that we see in many submissions. And if done appropriately and appropriately validated, it's generally held to be more or less a confirmation of what you're seeing is actually what you're getting. But based on a technical basis, it is subject to a slight amount of criticism, which the sponsor hopefully will correct in their study.

Now, the results of this study that you see in the table here, -- and this is again from the article -- I found a few things about this to be quite interesting.

The first thing that struck me is you see they measured both compounds. They measured Carisoprodol and meprobamate in their subjects. And they've divided the results into two categories: extensive metabolizers -- nine of the ten they called extensive metabolizers -- and one which they identified as a poor metabolizer. That's the first interesting thing.

The other thing that struck me is if you see under the very first line under "Carisoprodol," the half-life of Carisoprodol is stated as 99 minutes, which I think is consistent with what others believe that they know in the literature. That means it's an hour and a half half-life.

That kind of struck me as a little bit strange because this is a drug which is given every six hours, every eight hours and from all that we know is effective over that entire time period. So it struck me as odd that we have an hour and a half -- with the parent being an hour and a half half-life, it's dosed on a much longer interval.

And there are a couple of logical reasons you might expect this, but basically it's a little unusual, although not unheard of, for a drug to have a short half-life and be dosed on a long time period. But it still led me to think that there may be something else other than the parent contributing to not only the effects we have talked about but perhaps the therapeutic effect as well. As you see, the poor metabolizer has a much longer half-life.

The rest of it really follows from just looking at the difference between the extensive and the poor metabolizer. But, as you see, there is an

extensive appearance, if you want, of meprobamate in these subjects.

In the nine extensive metabolizers, we see maximum concentrations of 18. I believe that's in micromoles per liter after about 220 minutes. And they kind of picked a time point at about 6 hours where they found that in the plasma at that time point about 92 percent of what they saw on a molar basis was meprobamate, the remainder of which was Carisoprodol.

Just to put these in perspective, this is the concentrations of meprobamate which we're seeing -- and you can go to the next one, where we'll see a graph of this -- were roughly in the range of what one might see after therapeutic dosing of meprobamate. It's kind of on the low side, the low end of the range that's usually seen, but it's consistent with the bottom part of the range that's seen with about 400 to 800 milligrams of meprobamate.

Now, to explain this, this line, the solid line with the open circles, comes down quickly. This is on a log scale, by the way. It comes out very quickly, very nicely with that hour and a half half-life, the parent Carisoprodol and the extensive metabolizers.

And, as you can see from that upper solid

line with the dark symbols, the meprobamate comes up, is very slow to come off. And it's still around at the end of the measurement period.

That's due to two factors. The factor is as the Carisoprodol is being eliminated, meprobamate is allegedly being formed. So we see a very slow formation, and we also see the meprobamate is supposed to have around an eight-hour half-life, much more consistent with a drug that would last eight hours.

So, as we see, it comes up. And it just kind of comes down slowly. So at least if you believe that this is an adequate representation of the general patient population or using population, you could expect that 80 or 90 percent, some majority of subjects or patients are going to get this type of picture.

However, a minority are likely to be poor metabolizers with defective metabolism. So you see a representative here where the Carisoprodol goes up and comes down very slowly because it's not being eliminated as readily since this is a poor metabolizer. And you see some formation of meprobamate but much, much less as a percentage basis than the extensive metabolizers.

The authors worked up this particular

individual and found out that this type of poor metabolism seemed to correspond to a poor metabolism of mephenytoin. And that's a standard probe to look at certain polymorphism of metabolism in certain people with 50 enzymes. That does not necessarily mean it's metabolized for the same thing, but it may just co-segregate with that.

So the question that this raises is that, at least if you believe this article, a significant portion of the population is likely to form quite a bit of meprobamate from this. However, there will be a small minority of subjects or patients which do not readily form meprobamate.

The question that I would raise is I'm not really certain of what the percentage is, although from this study, it appears that it's probably a majority.

Two other points I'd like to make that came up while I was listening to the presentations -- well, one other point. We have a lot of reference to animal studies.

The sponsor, on one hand, has stated that the animals they've looked at, which I believe are the dog and the rat, do not readily metabolize Carisoprodol to meprobamate. And, at the same time,

they use the animal studies of addiction to prove that this is not an addictive compound or an abusable compound.

Really, if the animals are significantly different in their handling or metabolism of this compound and do not form meprobamate; whereas, humans do, then those animal studies are really not applicable, strictly speaking. So you have to use a lot of care in interpreting animal studies where the animals don't metabolize the same way as humans.

The other thing is a methodological point that in subsequent studies that we do, we have to be very careful when we bring in subjects to do the studies, that we don't purposely or inadvertently pre-screen and have a majority of subjects which are poor metabolizers of, say, mephenytoin, which would automatically give you a population that formed very little, comparatively little, meprobamate. So that's another consideration when we're planning new studies. Whether we pre-screen or not, they should adequately represent the population.

That's my conclusion.

CHAIRMAN SCHNEIDER: Questions? Dr. Wright?

DR. WRIGHT: You covered this, but I just

want to get a feel for it. You've described that $C_{max}$ for the meprobamate, the metabolite identified as meprobamate, is at the bottom of the therapeutic range?

DR. CONNER: It's within the -- for instance, the authors of this paper state that the normal concentrations of meprobamate after a 400 to 800-milligram dose are about, I believe, 20 to 100 I think is the range they state. And these concentrations range about 15 to 25 or so.

So it's up there into what's considered the bottom part of -- I wouldn't call it a therapeutic range. I'd call it what one achieves when one gives a dose of meprobamate, which is maybe different than what we normally term "therapeutic range."

DR. WRIGHT: The only question I have is that to achieve a dose that would have a psychoactive effect in the gabinergic agent-tolerant patient, you may be talking about many multiples --

DR. CONNER: Yes.

DR. WRIGHT: -- of the recommended Soma dose.

DR. CONNER: Which if the estimate that we heard this morning of all the doses and dosage units that people seem to have in their possessions, both

users and distributors, people would seem to be taking multiple doses to get the effect that they're looking for.

I don't really -- well, I can't comment. I can speculate that I don't really think you might see that effect by taking one or two Carisoprodol tablets. You might have to take quite a few to get the effect.

CHAIRMAN SCHNEIDER: "Quite a few" being what? Five? Six at a time? Four?

DR. CONNER: I haven't done the experiment on myself. I don't know.

CHAIRMAN SCHNEIDER: Is there any racial difference? Was the person who was the slow --

DR. CONNER: I don't know from the -- you know, this is a journal article. And it wasn't even a very long one. So I don't have a lot of the details that we usually see in reports that come in to us in submissions. We don't have the journal articles, unfortunately.

CHAIRMAN SCHNEIDER: Okay. Dr. de Wit?

DR. de WIT: I have a comment before you go.

DR. CONNER: Sorry.

DR. de WIT: It seems to me that even if

meprobamate does appear after the Carisoprodol, then I don't think that's an absolute indication that this is a drug that has potential to be abusive.

If we look at the rate of onset of the appearance of the meprobamate, it doesn't peak until about four hours. And our other information about abused drugs indicates that it's a rapid onset of the agent in the CNS that accounts for abuse.

So, even if there is significant meprobamate metabolized, I'm not sure that that in itself is an indicator that the parent drug here will be used.

DR. CONNER: Yes. It really depends on the pharmacology, which I think we're going to be talking about later. As you probably all know, abusable substances are the ones that are most preferred and many times have a quick onset. It's that quick up that usually people are looking for.

However, you can predict from this that given multiple doses, you accumulate quite a bit of steady state meprobamate. And it probably has an effect if you believe that this causes habituation and withdrawal effect; whereas, they're going to be exposed to quite a bit of this, whether that's a desirable thing to an abuser.

DR. de WIT: Right. And whether that's relevant to abuse at all is a separate question.

DR. CONNER: Right, right.

CHAIRMAN SCHNEIDER: Ms. Cohen?

MS. COHEN: Dr. Klein.

DR. KLEIN: Well, this does follow up with Dr. de Wit's comment. I think that that principle of rate of onset for a potentially abusable drug is a guideline that we follow for new drugs that are being placed on the market because we try to predict what the abuse potential is for those drugs.

But for a drug that's been on the market for almost 40 years, we try to do a balance of the pharmacology, the pharmacokinetics, and the indicators of actual abuse.

CHAIRMAN SCHNEIDER: I'd like to make a comment about this. There are street drug users or abusers. And then there is that population of the non-street abuser, the person who gets habituated. And there are different qualities that each of these people look for. So I think we have to keep that in mind.

Ms. Cohen, did you have a comment?

MS. COHEN: Yes. I have a few questions for Dr. Wright. Do we have all the work that's been

done on this drug from the beginning until now? What kind of information do we have that might be helpful to us?

DR. WRIGHT: Stay tuned, and we will be presenting it over the next hour or so.

MS. COHEN: Really?

CHAIRMAN SCHNEIDER: Hang around. Go ahead.

DR. WRIGHT: I won't say that it's all, but it's quite a bit.

MS. COHEN: Okay. Thank you.

I wanted to ask Dr. Hutchinson something from DEA if I could.

CHAIRMAN SCHNEIDER: Go ahead if she will approach a mike. Thanks.

MS. COHEN: In looking through the literature here, I see some things on the emergency room, the more females are affected than males. I'm going to try and ask a question. I hope I ask it properly.

Have you seen people in comas or in toxic condition who have taken this product? And is there a real possibility this drug reacts strongly with other kinds of medication? And have you seen any other kinds of -- I have a radio program, and I know

I ask too many questions. Have you seen any of the muscle relaxants do the same thing?

DR. HUTCHINSON: I have some indications from the STRIDE data. There are indications in the federal data that patients have stated for the record that they have gone to a doctor and this doctor has attempted to get them addicted to Carisoprodol or they felt that the doctor was attempting to addict them. And then the doctor would leave and these people would be dependent on the Carisoprodol and would end up in an emergency room.

I believe there were four people that I know of in one case report. They described their symptoms as severe and lasting for one week.

I know this is minimal. I believe there are some reports in the scientific literature that state that there is some dependence associated with this drug.

And your other question?

MS. COHEN: Have you seen other muscle relaxants do the same thing? Has that been your experience?

DR. HUTCHINSON: I can't answer that question.

MS. COHEN: Okay. Okay. I guess the

thing that is troubling to me is that if one takes this medication and something else is prescribed, then the chemical interaction might change this into something far different.

I'm not a scientist. My husband was. But that's the feeling that I get from the discussion. If I'm wrong, please tell me.

CHAIRMAN SCHNEIDER: Dr. Wright?

DR. WRIGHT: I won't say you're wrong, but the emerging pattern appears to be that there are -- so far most of the cases have been described as people who have an established pattern of drug-seeking or drug abuse behavior who seek out this drug because other drugs are not available to them or are less available to them. But we have a ways to go in the story as yet.

MS. COHEN: Thank you.

CHAIRMAN SCHNEIDER: Any other questions?

(No response.)

CHAIRMAN SCHNEIDER: Dr. Conner, thank you very much.

Our next speaker is Dr. Arthur Raines, Professor of Pharmacology, Georgetown University School of Medicine. Dr. Raines?

**THE PLACE OF CARISOPRODOL IN THE MANAGEMENT OF PAIN**

**DR. RAINES: I had the occasion perhaps 20 years ago or so to work with Dr. Irma Hobart and Cedric Smith in reviewing some of the studies that have been submitted in response to the DESI, designations, of less than effective for this class of drugs, essentially acting skeletal muscle relaxants.**

**Could I have the prior slide, please? There's one before that. Oh, do I have the gizmo? All right.**

**This is the group of drugs that we're talking about. And they derive from mephenesin, which was a compound that was available in the '40s. Actually, it was marketed as a skeletal muscle relaxant, produced paralysis in animals without interfering with neuromuscular transmission. And, therefore, this novel action seemed to be something that might be useful in muscle spasm.**

**Unfortunately, the drug had a very short half-life because it was glucuronidated on this hydroxy group. And, as a result, this group was masked with a carbamate ester instead. And the mephenesin carbamate was a marketed drug. I don't know that it's still marketed. But it's a compound which has a longer action than the mephenesin.**

The carbamylation, unfortunately, seems to have diminished its specificity. And it tends to be more of a global CNS depressant closely chemically related to the mephenesin carbamate is methocarbamal, Robaxin, which is shown over here.

Now, the drug which is under consideration now, Carisoprodol, is n-isopropyl meprobamate. Here is meprobamate, and here is Carisoprodol with an n-isopropyl. So it's N-alkyl derivative of meprobamate.

Now, one of the problems that we had in evaluating the studies for efficacy on this group of drugs, including Carisoprodol, was that these are not a highly effective group of drugs. If they're active, they're kind of feeble.

After years of grappling with the difficulties in demonstrating efficacy in skeletomuscle spasm -- and let me just allude the reasons for the difficulty were several.

One was the conditions for which the drugs were being used and evaluated at, say, one, four, and seven days of treatment were conditions which were relatively self-limiting, strains, sprains, muscle trauma, charley-horse of one sort or another.

And so in many, many of the studies, the

drugs were not superior to placebo. The drugs were not superior to analgesics. And the drugs were not superior to physical therapy.

It's for that reason the way they're labeled. They're labeled as adjuncts to physical therapy, rest, and other interventions. So I think one of the important things to come away with with this group of drugs is they're not a group of drugs with a high order of efficacy.

And, in fact, Dr. Craut, who was then Director of the Bureau of Drugs, declared them effective because it was becoming increasingly difficult to know what to do with these things. And so using the authority in the office, he just said, "They're effective, and let's leave it at that."

I will read the indications for Carisoprodol just to remind you. You may very well have a label with you. It's indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute painful skeletal, musculoskeletal conditions.

The mode of action of the drug has not been clearly identified but may be related to its sedative properties. Carisoprodol does not directly relax tense skeletal muscles in man. So this is

another issue that has dogged this drug and the others in this family. And that is that there has never been a demonstration that there's anything selective about the ability of these drugs to reduce muscle tone.

It may very well be part and parcel of a sort of a general central nervous system depression. So that in much the same way that if you reduce activity level or in the extreme, if you produce sleep with a barbiturate, of course, you get muscle relaxation.

So this has certainly been one thing that was a thorn in FDA's side. And I tried to help them with the problem, but the problem just didn't want to go away for the reasons I've just described to you.

I know that you've heard about the pharmacokinetics, but I have a couple of slides to make a point. For one thing, this stick figure of the structures is one in which there are a number of related drugs, Carisoprodol, meprobamate, tybamate, and a drug which had been originally thought to be somewhat antihypertensive, mebutamate. I don't know whether these are still marketed.

Felbamate -- I've added this to this slide -- is a related drug which is of value in the treatment of seizure disorders.

The metabolism you've just heard about. The metabolism is analogous, if I could just go to this slide, to the metabolism of diazepam, where you have an N-alkyl group, in this case a methyl group.

And the compound can be N-dealkylated to nordiazepam -- in this case, the alkylation leads to meprobamate -- or it can be hydroxylated, in this case to three hydroxydiazepam, which is temazepam, also active. And the hydroxylation in the case of Carisoprodol takes place on the side chain of the Number 2; in other words, on that normal propyl group.

I was going to say some things about the study that was just discussed with you, but that was very, very nicely handled by the prior speaker. And so I won't get into this except to reiterate a point that was just made. And that was that if you have a drug with a half-life of one and a half hours and it's converted to a drug with a half-life of something like ten hours, the literature would give you a range of something like 6 to 17.

What's going to happen on chronic exposure is that you're going to get cumulation of the drug with a longer half-life. I haven't done the calculations, but it would be substantially higher than would be the levels of the administered drugs.

So what we would see under those circumstances -- you can turn the lights on now and the slide off, please. What one would see under those circumstances is an oscillation in the Carisoprodol dosing levels and a steady cumulation to a steady state level of the drug with the longer half-life.

So with regard to, say, tolerance and dependence, one would presume that sustained higher levels of circulating meprobamate would contribute to the ability of the drug to cause physical dependence because those levels would be higher and they would be sustained.

I think I'll stop now. And if you'd like me to elaborate on any of the issues that I've raised, I'd be happy to do that.

CHAIRMAN SCHNEIDER: Questions?

(No response.)

CHAIRMAN SCHNEIDER: I thank you very much, sir.

DR. RAINES: Thank you.

CHAIRMAN SCHNEIDER: Our next speaker is Dr. Peter Staats, Chief of Pain Medicine, Johns Hopkins University.

DR. STAATS: Thank you, Mr. Chairman.

As the Chairman said, I'm Peter Staats.

I'm the Chief of the Pain Medicine Service at Johns Hopkins University. In that capacity, I oversee the evaluations of about 10,000 hospital days a year for acute pain and about 5,000 outpatient visits a year for chronic pain.

My expertise is primarily in the management of chronic pain and the role of medical management as well as other therapies in the management of chronic pain. However, I do know something about the management of acute pain as well.

The primary reason that people would want to use muscle relaxants is for acute muscle strain. Although it's hard to get a good handle on how big of a problem this is, muscle injuries occur to about 24 million Americans annually.

The most frequent cause of chronic and permanent disability, 25 percent of the population has to limit their activities and seek medical care. and it has prompted 70 million office visits a year. Now, this is not just acute muscle strain, but this is all musculoskeletal injuries.

Next slide, please. This accounts for a large number of disabilities, 15 percent of disabilities. And these are somewhat old data from 1986, but it reflects 35 million individuals. This is

estimated total cost of about $70 billion in terms of disability and injury to musculoskeletal disorders.

Now, there are a number of approaches that we use for the acute muscle strain. Rest is very commonly recommended, psychological approaches, rehabilitation medicine. Medical management is probably the mainstay. And that's why we're all here today, to talk a little bit about that.

Some people do nerve blocks and trigger points and epidural steroids. And on occasion I think we do surgery. And my bias is that we do a little too much surgery for acute muscle and back injury.

Next slide, please. Now, it's important for us to define what we're dealing with. Pain is not just a biological event. There's an old Descartian model of pain comes from the periphery and goes straight up to the brain. And it's all a biological event. We know that's not true.

Pain is a complex event. It's an unpleasant sensory and emotional experience associated with actual or potential tissue damage or defined in such terms. This is the official definition from the International Association for the Study of Pain.

Now, it's important -- and I'm sidetracking a little bit here because I think this is

important and will affect how we look at medical management in a variety of therapies. It's important to understand that pain has a very complex and strong emotional component.

Next slide, please. I've recently written a new theory about what is pain that incorporates the emotions. Emotions are very central in the presentation of pain. It has its basis in biology. And I'm not denying at any level that there is a biologic component to most individuals with pain. However, there's a strong emotional component as well.

And, importantly here, pain abides by the principles of classical conditioning. There are things that can be given to become reinforcing. And things can be given to minimize emotional state.

Next slide, please. And this is kind of a summary slide of what happens in an individual with pain. There's usually a biological or nociceptive state. There is an emotional response. That can be conditioned, be it language, psychological, workforce factors, financial concerns. Anxiety is a big one. All will affect the emotional state, which affect pain.

Now, next slide, please. Okay. We have traditionally said if it hurts, take a pill. That's

kind of what our medical model has been. Wait until it hurts because we don't want you to take too much. If you take too much, you'll become addicted to this stuff. And only take one pill every six hours to kind of avoid that.

It's fine what we know about the duration of action of a lot of the analgesics that we use. This is what happens out there in the community. This is what people say.

Next slide, please. Okay. So the problem is the principles of classic conditioning, short-acting analgesics or short-acting muscle relaxants, or whatever we want to call it there, will through principles of classical conditioning become reinforcing.

This may take months. This may take years. I don't know how long it will take, but it happens quite frequently when we do this. And this is what I think leads to abuse of the variety of substances.

Next slide. This is a slide that I have a few nomers here, but it's basically here's a nociceptive stimulus that affects the personality and what has been also termed the basic behavior repertoires. This is, it affects the individual's

pain and emotional state, and it gets someone to take a pill.

If someone takes a pill, this pill and all the behaviors around taking this pill through principles of classical conditioning will become reinforcing. This again affects the emotional state. And over a long period of time, this is how patients develop some dependence on short-acting drugs.

Next slide, please. Okay. So my opinion is that muscle relaxants may be important in the management of acute muscle strain, should be used as an adjunct to rest and physical therapy, but there really is a very limited role in the management of chronic pain.

Next slide, please. I'm sorry about the misspelling here. Now, Carisoprodol, however we want to say it, does produce muscle relaxation in animals by blocking interneuronal activity in the reticular formation. This is also where we know emotions are processed, further support for what I indicated about principles of affecting the emotions.

The onset is relatively quick. It lasts four to six hours. It does cause sedation in many patients that I have seen. And it is not known to cause directly skeletal muscle activity, relaxation.

Next slide, please. Now, we need to make sure that we're all on the same wavelength about what is addiction and what is abuse. Addiction is an abnormal behavior pattern of drug abuse. It's taking medications to get high. It's taking medications for other than pain relief. It's going from doctor to doctor. One of the speakers earlier today mentioned doctor shopping. And it's taking the medications in spite of known harm. It's important that we make sure that that's the definition that we're going with.

Next slide. This is opposed to physical dependence, which is a normal pharmacologic response or physiologic response to chronic medical therapy. It doesn't matter if we're talking about opioids. It doesn't matter if we're talking about the anti-seizure medications. Patients can become physically dependent.

And if you abruptly stop the use of Tegretol, for example, in someone who has never had a seizure in the past, those patients will go through withdrawal. This is important that we don't confuse this with addiction because there are a number of -- I would say that a large percent of the patients that we are calling addicts, it's really pseudo-addiction, where they're looking for pain medications because

their pain is not adequately controlled.

Next slide. Now, the concern of addiction or abuse when you're talking about muscle relaxants is it does cause relief of pain for some individuals. It does cause central nervous system depression.

It does occur quickly so in a time-contingent manner, it becomes reinforcing. Muscle relaxants are for the most part that we have short-acting and require repeated dosing and repeated trials to maintain an effect.

Next slide. Now, I think we've heard a little bit about iatrogenic addiction and saying, "Doctors are getting me on these medications. And then they're getting me addicted to it." I would say that this does happen, but I feel that it's rare.

In the model where we're using short-acting analgesics, pill-taking behavior can become reinforcing. There is a well-known relationship between the time-contingent versus pain-contingent taking of the drugs.

And if we make everybody take the pill when they have pain, over a period of time this pill will become reinforcing, regardless if it's a centrally acting muscle relaxant or an opiate or an anti-seizure medication.

So through classical conditioning, these analgesics become reinforcing. And it takes many, many pairings. It doesn't happen on one pairing. It happens over months to years.

Next slide, please. I've stressed this issue because I think this is important in how we look at scheduling of this substance. I don't believe that there's a problem if the physician is monitoring the patient closely.

In following their patients, these patients will not become addicted to the medication. It's over an extended period of time that we have to have some level of concern.

So a better way is to follow principles of modern behavior theory, use long-acting analgesics whenever possible. Now, it's certainly not possible every time, but it's something that we should strive towards.

We should also know that there's very little data supporting the use of muscle relaxants in chronic pain for an extended period of time. I've reviewed the literature on that, and it's just not there.

So we need to look at other options if someone has chronic pain because we have very good

therapies for chronic pain, of which muscle relaxants should not be considered one of them.

One needs to avoid the pain-contingent use of analgesics as much as possible and maximize time-contingent use. Understanding the pharmacology of the drugs will allow us to give the therapy when it's needed.

Next slide, please. This would be an example of that. Try to knock out the nociceptive stimulus without giving the reinforcers with it, without taking a pill contingent on having pain and then subsequently pain relief.

Next slide. The advantages are that there are fewer peaks and fewer troughs. Fewer troughs would be associated with: better pain relief; decreased side effects of peak serum levels; -- so there would be no high -- and minimizing, as I said, the time-contingent relationship, taking an analgesic.

Next slide. Okay. It's my opinion again that the short-term use will not cause significant problems. The long-term use can lead to problems with the pills becoming reinforcing. And for patients with chronic pain, they should not be on the short-acting analgesics unless they've had a really comprehensive approach to the management of their chronic pain.

Next slide. We do want to give our patients pain relief. So there's this conundrum here. We want to give the patients pain relief when they need it, but I think we need to recognize that the manner in which we are giving medications can lead to a problem with abuse. And over an extended period of time in patients with chronic pain, these patients will develop psychological and behavioral problems associated with short-acting therapies.

Next slide. Now, I have to say that I rarely use Soma for chronic pain. as I indicated, the literature does not support the use in patients with chronic pain. But my practice is a practice of patients who have had pain for seven or eight years.

I've had patients who come to the Johns Hopkins pain program on Soma. And it is very difficult to deal with a lot of these patients. They really like their Soma. They feel that this is what they need. Even though they are doing very poorly, they have come to believe that this drug is what it is for them, this is it.

But they wouldn't be coming to see me if they were doing well. So there's a dichotomy here. And I frequently have to admit the patients to detox them off of the therapies.

This is contrary to what we've heard today of having no problems with addiction or physical dependence to the therapy. That is not my clinical experience.

Next slide. Okay. So, in summary, I'd like to say that I think that Soma and the other muscle relaxants have a very limited role in the management of chronic pain.

There may be a role for it in the management of acute pain that I do not dispute at all and that I believe that long-term management with any of the short-acting analgesics or muscle relaxants may lead to problems with abuse. And this should be monitored by their physician. That means the patient should be going in and seeing their physician and not calling up for a prescription.

That would be the only interaction that they have with their physician. And so they should be evaluated on some period of time that would be considered reasonable by their physician to follow them and make sure that they're not developing problems with abuse.

And I thank you. Again, I wanted to indicate that I'm coming to speak with you as a clinician with expertise in chronic and acute pain.

And primarily I wanted to talk to you about principles of how we manage patients with medications as well as what is my experience with the muscle relaxants. Thank you.

CHAIRMAN SCHNEIDER: Thank you, Dr. Staats.

Questions? Dr. Khuri?

DR. KHURI: As another clinician, I greatly appreciate your clinical perspective and the sensitivity with which you deal with your chronic pain patients, not an easy group to deal with, particularly emphasizing the importance of belief systems.

You mentioned, though, that many patients -- it was on your slide -- like their Soma and you've had to detox them. Can you give me an order of magnitude of numbers with numerators and denominators?

DR. STAATS: The total number of patients who are on Soma I would say is a small number.

DR. KHURI: Yes.

DR. STAATS: If I said that I have four or five thousand patients coming to see me, I would say less than five percent of them are on Soma in particular.

The problem I have is that these patients after they have been on it for an extended period of

time are quite difficult to deal with. And a high percentage of these patients are the ones that I either need to admit to the hospital for detoxification or have a problem getting off of the drug. So it's a higher percentage than the rest of my population.

DR. KHURI: It is difficult to dislodge belief systems, but can you tell me over eight years how many you've had to detoxify?

DR. STAATS: I would say more than 10, less than 50.

DR. KHURI: Thank you.

CHAIRMAN SCHNEIDER: And may I ask you to extend that and tell us the problems of your detoxification or what methodology you might use?

DR. STAATS: Well, we bring them into the hospital for a comprehensive program. And we will slowly taper them off of the medication. We have not seen seizures, which has been reported. We have seen mostly behavioral problems of the patients indicating that they're doing much worse for a period of time coming off of it.

DR. KHURI: Are these patients who tend to abuse other drugs and take non-prescribed drugs?

DR. STAATS: Not usually. They are not

usually patients who take non-prescribed drugs. They usually have been prescribed by their physician. And the physician has just gotten to the point where they're very uncomfortable with what's going on, but they keep escalating the dose because the patient says, "You know, Doc, I need this, but I need more." And they have been escalating and escalating and escalating to a point where they're not operating in a successful pattern any more.

DR. de WIT: I just have one minor comment. Could you document that that was the only drug that they were taking chronically at the time that you detoxified them?

DR. STAATS: Frequently it is not the only drug that they are taking. They are frequently taking other drugs as well. And I'm just indicating that, as we said, belief systems can be sometimes difficult to differentiate.

They are frequently on other analgesics as well. They are frequently on short-acting opioids as well.

DR. de WIT: Okay. I just have a small comment. I was interested in your theory of what makes a drug a reinforcer. I was concerned, though. By that reasoning, then aspirin should be a highly

abused drug if it's the pain relief that makes the drug sought after and abused.

DR. STAATS: Well, there are different ways that a drug can become a reinforcer. A drug can become a reinforcer by removing a negative emotional stimulus, which is pain. It can become a reinforcer by making a high or a relief of anxiety or a relief of a negative emotional state or induction of a positive emotional state. Either one of those would be reasonable.

A drug like aspirin functions largely by inhibiting prostaglandin synthesis. In my laboratory, we have shown that a lot of the effect of PGE2 specifically functions by sensitizing nociceptors.

If we take away the PGE2, we will still have pain, but it takes away the sensitization. And it lasts for an extended period of time, hours. It doesn't work immediately, in a quick time-contingent manner. It works in a delayed fashion by affecting PGE2 production.

CHAIRMAN SCHNEIDER: Dr. Strain?

DR. STRAIN: You asked my question. Thanks.

CHAIRMAN SCHNEIDER: Thank you.

DR. YOUNG: Can I ask a question?

CHAIRMAN SCHNEIDER: You certainly may, Dr. Young.

DR. YOUNG: Can you give us an idea of the doses of the product that you've experienced in these 10 to 50 patients, what dose range and the frequently with which they were taking the medication?

DR. STAATS: Frequently it's taking medications of about 700 milligrams every 4 to 6 hours.

DR. YOUNG: Okay. And does the detoxification program include termination of administration of the other agents the patients are using?

DR. STAATS: That's a good question. And I have to say we have changed over time. It used to be the bias that opioids wouldn't work for chronic pain. And we would detox people off of everything.

The literature has really evolved to suggest that the use of long-acting opioids is effective for some patients. And I think that we have moved towards taking them off of muscle relaxants and short-acting benzodiazepams and maintaining the use of long-acting opioids.

DR. YOUNG: Such as?

DR. STAATS: Such as methadone, M. S.

contin, oxycontin, fentanyl patch, levorphanol. We maintain those analgesics as there really is significant data to support that use.

DR. YOUNG: And what pharmacological adjuncts do you use in the detoxification program? You indicated some patients are also using short-acting benzodiazepines?

DR. STAATS: We do use some clonidine, but I would say the predominant way is slowly tapering them off their drug.

DR. YOUNG: And what's your dose taper schedule?

DR. STAATS: Twenty-five percent of the previous day's dose. It's pretty typical.

CHAIRMAN SCHNEIDER: So a four to five-day come-down?

DR. STAATS: That would be quick. Twenty-five percent of the previous day's dose.

CHAIRMAN SCHNEIDER: Oh, the previous day's dose. Okay.

Ms. Cohen?

MS. COHEN: I have two questions.

CHAIRMAN SCHNEIDER: Use your mike, please.

MS. COHEN: Oh, gosh. I know that.

Do the patients understand the medication they're taking? Has it been discussed with them by the physician and this laid out what could happen? And does the physician know what he's doing when he uses it as a prescription?

DR. STAATS: I would say that invariably the physicians feel that they're doing the right thing. And the patients come to them and say initially, "Gee, I'm doing a little bit better. This is great."

But I would not say that the physicians are doing the right thing. And I don't think that the patients have been counseled always about the possibilities of what's the reality of the use of muscle relaxants in chronic patient.

MS. COHEN: But therein lies the problem. It's the detail man that gives them the information or do they read the PDR or do they read the PDR or do they read the inserts? How do they know this is appropriate if they haven't read the literature?

DR. STAATS: I can't answer that.

MR. LLOYD: Have you had experience with patients on long-term meprobamate? And have you had to detox any of them? And if so, how do they compare to the patients you've detoxed on Carisoprodol?

DR. STAATS: I have no experience with that.

DR. STRAIN: The patients who report or their physicians, physicians' report, that they have had to increase the dose, do those patients report developing tolerance to the muscle-relaxing effects or what effects do they report, the results and meeting dose escalation? Is there tolerance?

DR. STAATS: One of the important things to understand about -- I'm not sure I'm going to answer your question here. I'm going to do my best here. One of the important things to understand about this therapy is very frequently patients are misdiagnosed and are diagnosed with simply a muscle strain that goes on and on and on and on and on.

And they begin to take their muscle relaxant for a secondary problem, which is the injury muscle strain, which may affect anxiety, which may take away the pain temporarily, but the problem is never solved.

And over a period of time, the dose does go up in some set of the population. I can't tell you what the *n* is at the bottom because I only see a small percentage of the patients.

It does go up. And so, by definition, the

dose goes up without seeing an effect over time in terms of relief of pain. So, in fact, there is some type of tolerance.

DR. STRAIN: Just to go back, let me try stating it a different way. For patients who have used increasing doses over time, have you asked any of them? And do they say, "Well, I liked taking two tabs. And so since two tabs made me feel good, I thought let me try taking four tabs because I wanted to feel twice as good" or did they say, "I took two tabs for a while, but then I wasn't getting that effect anymore. So I had to go back to my doctor and say, 'I need more.'"

DR. STAATS: That's difficult for me to tell you that.

DR. STRAIN: Okay. Let me ask a different question. When they've come in to be detoxified, you said you've seen no withdrawal seizures.

DR. STAATS: Correct.

DR. STRAIN: Have you seen withdrawal symptoms or signs of any sort? Has there been any sort of withdrawal?

DR. STAATS: I would say I haven't seen the typical "Gee, my skin is peeling off, and I'm sweating and diaphoretic." That I haven't really

seen, what we think about with opioids. But I have seen that patients are temporarily much worse. They can be worse. There may --

DR. STRAIN: Can you just --

DR. STAATS: They display much more in the way of pain behaviors and say, "I'm hurting a whole lot more, my muscle, my back." And what I'm really thinking about is back pain because this is really the largest percentage of the patients who get this therapy that I see.

They're much more irritable for a period of time and sometimes more anxious.

DR. STRAIN: Sleep disturbances?

DR. STAATS: Yes, sleep disturbances.

DR. STRAIN: Dysphoria?

DR. STAATS: Dysphoria, yes.

DR. KHURI: I continue to be interested in this same group of less than five percent of your total patients certainly that get in trouble with Soma. I'm sure that running a good pain service, psychiatry, and good psychiatric diagnosis is an important aspect of it.

we have learned that these people are not necessarily poly-drug abusers or druggees. What about their psychiatric status and diagnosis? I'm sure

they're evaluated. Is there a high percentage of anxiety disorders, thought disorders? And are psychotherapy and counseling, also alluded to by Ms. Cohen, part of your regime of detox?

DR. STAATS: We have a multidisciplinary approach. Many of the patients are admitted to the inpatient psychiatry program and have been for many years there. They admit about 125 patients a year, something in that range, not just for Soma but for a complex set of problems, some of which are detox. others are not.

I don't know about the patients who walk into the door of my clinic. I can tell you the national experience is about 70 percent of the patients who walk into a multidisciplinary pain center have a diagnosis that would be consistent with depression, have a diagnosis of depression.

A large percentage of patients who come into a multidisciplinary pain center, as opposed to patients treated in an HMO, have another psychiatric diagnosis as well, not major thought disorders, but affective disorders as well.

So the patient population that I see is, in fact, different than what we see in --

DR. KHURI: I'm not speaking about your

general practice. I'm speaking about the people in trouble with Soma.

DR. STAATS: I can't say that I think it's different. And I don't have that number, but I do not think that it's different than the general population. I do not think that they are schizophrenics or major affective disorder. that's not my impression.

DR. KHURI: Primarily for depression and anxiety?

DR. STAATS: That's hard to tell because so many of our patients have depression already. And so it would be hard to tease that out.

DR. KHURI: thank you.

CHAIRMAN SCHNEIDER: Ms. Cohen?

MS. COHEN: Do they have unrealistic expectations? Is that part of the problem that they're not sharing in the process of the diagnosis and what the program is but they're told, "You take this? And, therefore, they think that automatically it's just going to -- particularly the back pain.

And I've been through it. It's prolonged. And maybe if it was explained better to them, they would understand.

DR. STAATS: I have to say that I think physicians in general don't deal well with the

management of chronic pain. They're afraid of prescribing opioids and other therapies. And for that reason, some inadequate therapies may be prescribed for chronic pain.

CHAIRMAN SCHNEIDER: May I take a little different tact of there's a well-known theory, if not a truism, in addiction medicine that people may be placed appropriately on a drug which can cause dependence; i.e., a narcotic for pain and anxiety, an anxiolytic for anxiety, and a hypnotic for sleep disorder, which is probably the worst thing to give for a sleep disorder, and that, although their symptomatology may go away under the effects of this and that the pathology for which they were given the drug in the first place; -- this is not a sleep disorder; eliminate that from our discussion -- i.e., the back strain, the knee injury, when the medication is stopped abruptly, that two things occur.

One is withdrawal symptoms appropriate to that particular drug and the length of time it was taken. And the other is -- and this is the thing I want to raise -- the issue of reemergence of the symptoms for which they took the drug in the first place, even though the pathology has cleared.

What has been your experience in your

patients that come in with the back pain persisting? Do you see find pathology in all of your cases? And what happens with them when you do your come-downs and take them off the medication?

DR. STAATS: I think the therapy that we use frequently is more of a substitution therapy, as opposed to always a removal of the muscle relaxants. We do use a lot of opiates in the management of our patients' pain and have documented a decrease in depression and an improvement in functional capacity and improvement in visual analog pain scores with that class of agent.

There are patients that we cure. They come in to see us, and we say, "Aha. You have this problem. We cure you." And when we take those patients off of their therapy, it has not been my experience that there is a reemergence of those symptoms if we cure the problem. I can't say that we cure everybody there.

CHAIRMAN SCHNEIDER: Sorry to hear that.

Any other questions?

DR. STAATS: I would like to say that my opinion is that a physician can use this drug, and it may have a role. But they should be monitored by their physician if they're on this therapy.

CHAIRMAN SCHNEIDER: Thank you very much, Dr. Staats. Appreciate it.

Our next speaker is Dr. Michael Kaplan, M.D., Ph.D., psychiatrist in private practice of rehabilitation medicine, Rehabilitation Team, Catonsville and Westminster, Maryland.

Dr. Kaplan?

DR. KAPLAN: Thank you very much.

First of all, I'm not a psychiatrist. It sounds a lot like psychiatry. It's called a physiatry.

CHAIRMAN SCHNEIDER: Sorry about that.

DR. KAPLAN: No problem. A physiatrist is a specialist in physical medicine and rehabilitation. And I'm in Catonsville, not Catonsville. And so I changed my whole talk today because --

CHAIRMAN SCHNEIDER: What's the third thing I did wrong?

(Laughter.)

DR. KAPLAN: I wanted to talk about some other drug besides carbamazol.

(Laughter.)

DR. KAPLAN: Just kidding.

Anyway, everybody talks about the different hats that they wear. I also have a Ph.D.

Some of our speakers today had a Ph.D. Mine's in neuroscience. I have an M.D., Board-certified in physical medicine and rehabilitation.

I am a strong clinical practitioner. That's my main thing, although I do have a faculty appointment at Hopkins in the Department of Anesthesiology and Pain Management and also at the University of Maryland in the Department of Anatomy and Neuroscience because I do that stuff. And I am here today to talk about the obvious problems.

I think there are a lot of issues that have come up that I think about in my practice. And I welcome the opportunity to discuss some of the things and try to formalize some of the thoughts that I've had.

Whether or not carbamizopral or meprobamate is a CNS-active drug or a psychoactive drug based on its scientific literature or based on different aspects of what is psychoactive and what is CNS-active I think are really almost unimportant issues in this particular case.

The fact that the medication isn't really completely understood in how it works or its mechanism of action again really isn't that important in the fact that we do understand that it works on the

reticular system, though.

And the reticular system is a very important aspect of the brain because the reticular system affects attention. It affects sleep. It affects basically our alertness. And I think that's well-documented.

So it's well-documented that it affects the reticular system. It's well-documented that the reticular system affects attention and our basically interaction with the real world. So in that way we know right away that this compound can have an effect on a person's mood, a person's attention, person's psychogenic effect or psychoactive effect. So this is an important consideration.

Another important consideration of this medication in my mind and in the clinical aspect as well as in the scientific part, but I don't do a lot of research on this or any research on this is the target populations we're considering here. We're considering target populations of people who are in pain but more specifically people who have some kind of an addictive personality or an addictive-prone personality.

People come to the office in pain. And you can put them on almost anything you want depending

on their personality as to whether or not they get addicted to this. People don't want to be on a narcotic. They don't want to be on anything that makes them feel funny. And, whether there's withdrawal or not, it will be easier to get them off of this in a period of a few weeks, whatever it is.

But there's a large group, a population of people that have an addictive personality and maybe not even have an addictive personality but are prone to that because of their life experiences.

People who come to you in pain come to you with a lot of other things. They don't like their work anymore. They're not enjoying their social habits anymore. They're not enjoying life anymore because they're in pain, especially when they're in pain for an extended period of time.

So, even if there wasn't a predisposition to having problems or an addiction personality, sometimes this can develop because their whole life has changed, their relationship with their family has changed.

So we have to consider the target populations. Asking one physician, "Well, how much percentage of your patients have this addictive personality? What percentage of the Soma?" it's hard

to say.

I'm in chronic pain specialty. So I see a lot of people that are taking medications for something like opiates or narcotics or Soma. Of those people, it's very, very difficult to try to wean them from Soma. And that's how I became aware of some.

We talk about our doctors misprescribing the medications. I've used Soma before, and I've never thought that I was misprescribing it. You can read in the PDR what it does, and you do it.

Someone said, "Well, this really helps. Can I take it another one a time of day? Can I take maybe two at one time? It helps me at bedtime."

And then after while, being in the chronic pain business, I'm saying, "What's going on with this stuff?" It seems like it's hard to get people off of it and they want it more frequently, people that don't come in with tattoos all over their bodies and smoking cigarettes and drinking. These are regular people that you don't really suspect, people that you don't suspect of having an addictive personality. So we have to consider the target populations as very important.

When you look it up and you start reading, "Well, what's happening with this medication? Is it

abusive or not? They say withdrawal isn't a major effect," you say, "Well, it's not too bad." But people want it.

It also has additive properties. You then start realizing as a clinician, not necessarily as a researcher, that these people are doing other things. Some of them have -- well, they're a social drinker.

What's a social drinker? Well, to them a social drinker isn't a beer on a weekend and maybe a case of beer or a six-pack of beer, frequently a six-pack of beer.

So there are other additive effects that start coming into your mind as a chronic pain physician and then start wondering about this medication.

Ease of availability is another consideration with this medication. And that's one of I think the major focuses why I'm here today. I think that the ease of availability should be decreased, which would help alert physicians to what this medication does to people.

So we shouldn't focus necessarily on the semantics. Is this a psychoactive drug by its scientific literature? Is this a CNS-active drug? We look in the PDR for any one of us. It can cause

light-headedness. It can cause feelings of euphoria because it acts on the reticular formation.

Its availability is quite pronounced. And this is a problem with many medications in general. We can call in prescriptions. Pharmacies are very busy. Doctors are very busy. They have their aides calling and things. You can call in a prescription. Who is to say that someone else isn't calling in the prescription?

When you have a written prescription in your hand, it makes it a little bit harder. I think in the older days it was hard to even bring in a written prescription. People didn't have computers. They couldn't go on their computer and make up a prescription. They had to go to a printing shop. Now anybody can write in a prescription. But, still, calling in the prescription makes it that much easier.

We talked about today in some of the questions that I heard we should go for further study. We should have identification of its misuse. We should have identification of its misprescribing.

These are nearly impossible things to really identify because, even used in a normal prescribed way, it has additive potentials. It's frequently misused. Patients use multiple pharmacies.

They use multiple doctors.

There's no way to track this now. Some people that are on prescription plans, you can track it because they have to get their insurance companies to pay for it. And that does happen.

But, then, people now are realizing, "Well, all I have to do is pay cash. All I have to do is go to a small Ma and Pa pharmacy that isn't on the computer network." Very few pharmacies are on large networks. And even those are almost impossible to track.

I have a patient that I'm suspicious of, and I want to find out if they're going to multiple pharmacies. It's nearly impossible. I've got to call everybody in hell to try to find out what they're on, got to call all the pharmacies, look it up. And it's very difficult.

And just the fact that I can call and have the pharmacist tell me information about a particular patient again talks about an ease of availability. Who's to say I can't call in a prescription? If I have the confidence and I'm not a physician and I want to call in a prescription, I can call in. They don't know. DEA numbers are easy to find. This situation with this particular medication is very easy.

So we have to look at what we see in clinical practice, not necessarily me as a Ph.D. or a researcher or in academics, but what do we see in clinical practice.

It's frequently seen in multiple medications. It's very difficult to taper. It's very difficult to track. People want more. Easily prescribed. It's easily called in. It is seen to be, at least in my opinion, in personalities that have addictive type of qualities. It does cause light-headedness and euphoria. This is clearly documented. And there are a couple of other things, but who knows?

Anyway, changing the classification of this medication I think is very important. Changing it to where it's required to have a written 'script, a written prescription, the patient has to come in, have a written prescription, signed by the physician and how much has several possible advantages.

It won't eliminate the abuse of this. It won't eliminate the misuse of it. But practically what it does is it alerts the pharmacist and it alerts the typical doctor, the typical physician that this is a medication that should be carefully looked at.

Right now there is no real classification

of this drug. And the typical physician, especially the HMO doctor or what they call the doc in the box, the urgicare, where people come down the street, someone says, "You know, I have Soma. I ran out. I've had this horrible pain." What's the big deal? Give them another 90, one tablet 3 times a day. That's 90. Go down to the other doc in the box. Get another 90. It's easily prescribed.

Physicians aren't alerted to it because there's no reason to be alerted to it. The FDA isn't alerted to it. Nobody is really alerted to it. So we have to have change the classification where it is a written prescription.

We can't taper these medications. Euphoria, light-headedness, dizziness. Even transient quadriplegia has been identified in the PDR. Coma, stupor, all of these things have been identified. Whether or not there is research, these are things that are in the PDR.

But if you read the PDR, there are a lot of possibility side effects for many different medications. And aspirin has been brought up. Well, should this be classified the same as aspirin?

Clearly aspirin isn't sought after for its psychoactive effects. It isn't sought after for its

CNS effects. So that problem shouldn't be a major issue here. It's perceived as a psychoactive medication. And for these reasons, we should really alert ourselves. The average physician needs to be alerted to this, to its abuse potential.

And I feel very strongly about it, not because I knew it was a problem dealing with chronic pain, from what I studied at pharmacology, but from what I found at just basic clinical practice. And by listening to speakers here, I feel even more strongly about that today.

CHAIRMAN SCHNEIDER: Thank you, Dr. Kaplan.

Any questions?

(No response.)

CHAIRMAN SCHNEIDER: I apologize for my three errors and thank you very, very much. Again, I want to thank all of the speakers who came in early.

Oh, a question? Sorry. I still want to thank you for coming in early.

MR. LLOYD: The reason I was reluctant is that this is not a question. This is a comment. And the speaker indicated that preference would be to change it to a compound or a classification that required a written prescription.

In today's hierarchy of requirements, that would be a Schedule II drug. And, as I have reviewed the material for the meeting, I haven't seen any indication or suggestion that being a Schedule II drug would be putting it into the same classification as morphine, that sort of thing.

DR. KAPLAN: Well, from clinical experience, again, what we were talking about before in terms of scientific literature and from clinical experience from patients, what they want these drugs to use, we have to consider: -- this was brought up -- Well, should we do this for aspirin, too?

This isn't aspirin. This is clearly an identifiable problem, regardless of the scientific literature. Otherwise, we wouldn't be here talking about it.

You and I are not the first ones to experience this. Peter Staats and I are not the first two clinicians to experience this. This is a common problem. That's why the meeting is held.

And it should be classified as a Class II drug.

CHAIRMAN SCHNEIDER: Dr. Khuri?

DR. KHURI: Also, just a brief comment. I feel moved to object to the term "addictive

personality" in this context because I would prefer what you know well as a neuroscientist to refer to biologic and genetic factors, genetic polymorphism that may make increased vulnerability to drug abuse and drug addiction in general.

I think to use "addictive personality" brings it into a moral realm, which is too often pejorative when we know that these are very complex illnesses. Just a comment for the record.

DR. KAPLAN: I think you're right as well. And I've thought of similar issues myself. I use that because that's the term that's used in the PDR and some of the other pharmacological texts. But, in reality, sometimes people that are taking alcohol, are they taking it because they're an addictive personality or are they taking it because they're really trying to self-medicate a problem?

DR. KHURI: That's a very long discussion, which is not germane to the discussion.

CHAIRMAN SCHNEIDER: Well, let me jump in here simply to --

DR. KHURI: But I think the PDR has dropped -- in the newer text, they've dropped "addictive personality" pretty well.

DR. KAPLAN: Yes. That's a good point.

CHAIRMAN SCHNEIDER: I think that the literature is replete that there is no evidence that there is, quote, "an addictive personality." It may be semantics, but there are certainly predispositions.

Dr. Wright?

DR. WRIGHT: I just want to make sure that I understand your position, Doctor. And I thank you for a very eloquent presentation. What I heard you say is that patients want it, at least some patients want it, it has additive properties to other CNS active agents, it is easily available, and it can be hard to get people off of it. You feel that somehow the threshold for access should be raised.

DR. KAPLAN: Should be raised. Well, definitely. That's one of the major issues to make it a Class II, because physicians do not identify this drug as a problem because it's not listed as a problem and it's easy to give out the same as you might give out for a typical position some of the nonsteroidal anti-inflammatories. Well, it helps. What's the problem?

DR. WRIGHT: Thank you.

CHAIRMAN SCHNEIDER: I pause for reflection. Thank you very much, Doctor.

Our final speaker --

DR. WRIGHT: Mr. Chair?

CHAIRMAN SCHNEIDER: Yes?

DR. WRIGHT: Just a question. Are we going to have lunch today?

(Laughter.)

DR. WRIGHT: And, if so, could you give me some clue as to when?

CHAIRMAN SCHNEIDER: The answer is hopefully.

(Laughter.)

CHAIRMAN SCHNEIDER: But I think that in polling the Committee prior to this session, we agreed that, if we could, we would continue to 1:00 or 1:30 and break at that time, which means that those folks could get on airplanes and trains faster.

So, if you don't mind having delayed gratification until between 1:00 and 1:30, we'd appreciate it.

DR. WRIGHT: I shall try to delay my gratification.

(Laughter.)

CHAIRMAN SCHNEIDER: All right. I think they're not going to hire me for this job again.

DR. WRIGHT: Other members of the Committee aren't throwing me treats.

(Laughter.)

CHAIRMAN SCHNEIDER: The next speaker is Dr. Silvia Calderon, Ph.D., Division of Anesthetic Critical Care and Addiction Medicine. Dr. Calderon?

DR. CALDERON: Thank you.

CHAIRMAN SCHNEIDER: I suspect the next time some of you folks come to a meeting I'm chairing and try to push it through, you'll bring a ham sandwich or reasonable facsimile for yourselves.

Dr. Calderon?

## FDA PERSPECTIVE ON DATA ANALYSIS

DR. CALDERON: Coming back to your comment on the presentation on Carisoprodol, I really don't know how I will do it. I'm really from the South. I'm from South America. So I have the strongest accent probably in the audience. So I will start talking about the FDA analysis of the data.

First, I would say that several acting muscle relaxants that we have been talking today are marketed in the United States either as single agents or as combination drug products. We have a Carisoprodol, bochofen, chlorozoxazone, cyclobenzaprine, dantrolene, diazepam, metaxalone, methocarbamal, and orphenadrine.

Bochofen and dantrolene are like the other

muscle relaxants, primarily prescribed in the alleviations of signs and symptoms of a spasticity. So from now on, I will take them out of our list. I will consider the other drugs as the primary indicators of muscle relaxants.

Carisoprodol was introduced on the market in 1959 as a single agent and was followed by a combination drug product, a Carisoprodol aspirin, in 1960. And since then, if I could have the second table, several other generic products have been introduced on the market and recently even three products in 1996: one single drug product and two combination drug products.

In order to address the issue, in order to address the DEA request, we tried to look for data in our databases, trying to look for warnings of any abuse with this drug. We mainly looked in the FDA adverse report system. We looked in the Drug Abuse Warning Network. We also took into consideration information obtained from the State Boards of Pharmacy.

In the FDA adverse reporting system, there are 421 reports as of August 1996, starting back in 1969. Dose reports gave us 210 COSTART terms. Those are terms used to describe the adverse events.

We have a list here. I have included in your packages the list of all the terms, but I have included in this table only the top 20 terms reported. It's true we have highlighted those that we consider they are related to dependency or abuse, drug dependency, overdose, overdose intentional, somnolence, convulsions, withdrawal syndromes, coma, syncope, stupor, drug dependency and addiction, suicide attempt, and tremors.

It's true that drug dependency accounts for 31 reports. And if you consider how old is the drug, we have considered few reports for that matter. But half of the reports have been reported during 1991-1995.

We also should say that the FDA adverse report system doesn't work very well with all drugs. We have a poor report for all drugs. Half of those 31 reports have been received during 1991-1995.

In half of the reports, Carisoprodol was used in combination with other drugs, drugs such as dextromethorphan, dextropropoxypene, meperidine, alprazalam. Even we have reports of use of Carisoprodol with somatriptan. So several other drugs have been used in combination. In the other half of the reports, it was used as a single agent.

Also, for the same period of time, for 1991-1995, we have received reports of ten deaths. Deaths in two of those ten deaths, Carisoprodol was used as a single agent. Every time that drug levels, levels of Carisoprodol, were detected, also high levels of the primary metabolite, meprobamate, were reported.

Once we have a number of adverse reports, we wanted to have an idea of what's the frequency of reporting. First, we analyzed the market, how many prescriptions are sold for Carisoprodol and the other muscle relaxants.

I have taken out of this comparison bochofen and dantrolene. And we could see that for 1992-1995 diazepam has 38 percent of the market share; followed by cyclobenzaprine, with 24; and, third, Carisoprodol, with 18 percent of the market share, the other muscle relaxants: methocarbamal, 8 percent; orphenadrine, 2; Carisoprodol, 8 percent, and metaxalone, 2 percent.

So what happened with the prescription sales of Carisoprodol in the last couple of years? We notice an increase in the prescription sales. And that's will be shown in the next viewgraph.

We could see when we compared

Carisoprodol, shown here in green, and meprobamate, in purple, and diazepam, in blue, it was an annual percentage change, an increase in prescription sales for Carisoprodol starting from 1991 to 1995.

Having this common denominator, we decided to calculate what's the frequency of adverse reports. In this case, we will get for a million prescriptions.

First, we considered all the adverse reports. This graphic differs from the one that was handed to you because I took off bochofen and dantrolene. They are not primarily used in musculoskeletal spasms.

So diazepam in the X-axis. We have adverse reports for a million prescriptions for 1992-1995. And the X-axis is selected drugs. We could see here that diazepam has the highest frequency of reporting compared to the other drugs: orphenadrine, cyclobenzaprine, methocarbamal, meprobamate, chlorozoxazone, Carisoprodol, and metaxalone.

But what happened with only taking into consideration those terms that describe adverse reports related to drug abuse? We grouped those terms. And we only account for reports accounting for dependency, dependency and addiction, including

overdose intentional, overdose accidental, and withdrawal syndrome.

In this case, we also have represented the adverse reports accounting for a dependency over those and withdrawal per million prescriptions. And we could see in this graphic that Carisoprodol has a comparable frequency of reporting to diazepam and is higher than that of cyclobenzaprine.

I will move on right now to data found in the Drug Abuse Warning Network. We obtained two kinds of data from this network. We obtained emergency department mentions, and we obtained drug-related death reports from medical examiners. I will first discuss the data regarding the emergency department mentions.

Here we also calculated the frequency of reporting, in the y-axis total emergency department mentions per thousand total prescriptions. Here the numbers were bigger. So we can compare for 1,000 total prescriptions. And in the y-axis, we represented the selected drugs.

We could see here also in this database that Carisoprodol and diazepam have comparable frequency of reporting. And it's higher than for the other muscle relaxants.

Also, our next question was: What's the motive for taking this drug? Who is the user? Well, first, we analyzed from the total cases we have seen that Carisoprodol has been associated in 25 percent of the cases reported, reported to the DAWN system. And it has been associated with other opioids also in 25 percent.

I would like to point out here that these opioids could be a prescription, obviously. I have considered here codeine, hydrocodone, other opioids. They are not indicators of abuse. And I have included here other drugs of abuse, like marijuana and cocaine. And in 25 percent of the cases, it was associated with alcohol and in the other 25 with other opioids.

Who is taking this drug? Where do they get the drug from? What is the age range? I have compared here for Carisoprodol and meprobamate. Always in this case these are expressed as a percentage of total number of emergency department mentions for 1990-95.

We could see that the motive for taking the drug, dependency accounts for 9.3 percent of the cases, 56 percent for suicide, 4.6 for recreational use, 15 percent reported for other psychic effects, and 15 percent for unknown or others. The fact that

we are reporting unknown is not as stated. When the report comes to the Drug Abuse Warning Network it's not stated, it will figure as unknown in our tables.

What's the age group? We have six percent of users 12 to 17; 14, 18 to 25; 31 for 26-34; and the majority of the users are 35 years old and older.

Legal sources? It's a split between legal, 50 percent; and unknown sources, approximately 42 percent: street, 29 percent, and other unauthorized sources, 4.9 percent.

When we compared to the use of meprobamate, we were able to see similar distribution in the motive for taking the drug, in the age group who is using the drug, and in the source. We could see a similar distribution. Although they are drugs, they don't have the same indication.

In the next slide, I will discuss the data obtained from the medical examiner reports. Here diazepam. Also, we have represented total medical examiner mentions for million of 1,000 prescriptions and in the x-axis selected drugs. We could see here the diazepam has the highest frequency of reports followed by meprobamate.

And I have included here another bar that represents the number of cases in combination where

blood levels of meprobamate and Carisoprodol were detected. And that accounts for half of the cases followed by Carisoprodol and cyclobenzaprine, bochofen and methocarbamal.

So what we can conclude for our results -- oh, well. I forgot the state boards of pharmacy data. I'm sorry. If we mentioned that we obtained from the state boards of pharmacy, we know that 27 states out of 49 have indicated knowledge of abuse of Carisoprodol.

Also, we have information that seven states have regulated Carisoprodol in Schedule IV. And they are under their own regulations. The states are Georgia, Hawaii, Kentucky, Massachusetts, New Mexico, Oklahoma, and Oregon.

And, to conclude my presentation, I will say that the frequency of reporting of adverse events related to drug abuse for Carisoprodol is comparable to that of diazepam and higher than that of cyclobenzaprine, that Carisoprodol and diazepam have a similar frequency of drug-related emergency department mentions.

I would like to point out that diazepam is shown in italics because it's a currently scheduled drug and it also has another indication. It's used

also as an anxiolytic. So it has another indication more than for the muscle spasms.

We can conclude also that Carisoprodol was associated with alcohol in 25 percent of drug-related emergency department mentions and also with opiates in 25 percent of these reports. In general, for Carisoprodol and meprobamate, there was a similar distribution in motive for use, age of users, and source.

In comparison with diazepam, there was a lower incidence of death reported by medical examiners for Carisoprodol. And Carisoprodol is currently scheduled in seven states.

That concludes my presentation.

CHAIRMAN SCHNEIDER: I thank you very much.

Questions? Ms. Falkowski?

MS. FALKOWSKI: Yes. I'm curious about your statement that it's similar frequency of emergency department mentions with diazepam.

DR. CALDERON: Yes. Well, I made the calculations. And, actually, I think I have an overhead. I thought of that question. If I can get it, approximately the counts are 60 percent for suicide. And you have the 14 --

MS. FALKOWSKI: Oh, you mean for the motive of use?

DR. CALDERON: For the motive of use.

MS. FALKOWSKI: Right, right. Let me point out there were 14,000 emergency department mentions of diazepam in '95 compared with 7,900 for Carisoprodol.

DR. CALDERON: When you divide it by the number of prescriptions, the common denominator is the number of prescription sales.

MS. FALKOWSKI: So then you're talking about --

DR. CALDERON: The drug's value for that period of time, that's what gave us the frequency of reporting.

MS. FALKOWSKI: Which is a rate --

DR. CALDERON: Is a rate, is a rate --

MS. FALKOWSKI: -- that you're talking about, a standard --

DR. CALDERON: -- of adverse reports related to number of prescriptions.

MS. FALKOWSKI: Thank you.

CHAIRMAN SCHNEIDER: Dr. Young?

DR. YOUNG: I have a question about how data are entered into these databases. If someone

comes in with a report of using this compound and diazepam and an opiate and alcohol, is that entered into --

DR. CALDERON: In the FDA database? Usually when you read the report, you have all the other drugs that they are using in combination. And, actually, I went one by one of the cases. And that's why I stated that in half of the reports it was used in combinations.

DR. YOUNG: And in those instances in which it's used in combination, are both drugs entered into the database separately?

DR. CALDERON: They are both drugs entered.

DR. YOUNG: And can you identify -- if you got a combination case --

DR. CALDERON: Yes.

DR. YOUNG: -- and the reason for use is dependence or the reason for use is a suicide attempt, is that also entered into both drugs or is there --

DR. CALDERON: We get motive for use from the DAWN data. And both drugs will be entered in the system.

DR. YOUNG: In the DAWN data --

DR. CALDERON: In the DAWN data, when they

refer to motive for use, it refers to the whole episode and --

DR. YOUNG: The motive for use, say if a suicide attempt was made with a barbiturate but that was combined with clonidine --

DR. CALDERON: Yes.

DR. YOUNG: -- or combined with aspirin, the suicide would also be entered in as aspirin?

DR. CALDERON: It will rank the first drug. It will rank probably barbiturate. They will rank. They will rank the drugs A, B, C, but they will be entered in, the three of them.

DR. YOUNG: So the motive for use could be attributed to any of the drug in the combination. And that's a problem. Right.

DR. CALDERON: Both systems have their limitations. And, if you could see, also I have reported in -- when you are going for the reports, death accounts only for two deaths since 1969. But when you are going actually through the reports, I went through the reports from 1991-1995.

You arrive to the number of ten deaths. So they have been reported either as overuse, overdose, or as suicide attempt, but the outcome was death.

DR. YOUNG: And in each of these cases, this was the only compound used?

DR. CALDERON: In two out of ten, it was the only drug used.

DR. YOUNG: But in every other case, you --

DR. CALDERON: The other cases they have been used mainly in combination with dextropropoxypene, I would say.

MS. FALKOWSKI: I'm curious about the DAWN medical examiner data that was contained in our packet of materials that showed somewhere on the order of magnitude of 40 to 45 mentions in the ME data per year since 1990.

I think in order to make more value of those figures, it would be helpful and almost necessary to have the total denominator of how many mentions. It's hard to look at a pattern over time without a denominator.

DR. CALDERON: The denominator of our frequency of reporting always has been the number of prescriptions. That's what your --

MS. FALKOWSKI: Even in the ME data?

DR. CALDERON: Even in the ME data. That's the only common denominator that we could find.

I would like to point out also that in the cases reported for Carisoprodol, in 62 percent of those cases, levels of meprobamate have been found in blood. That's why in the medical examiners' reports, you will see Carisoprodol and meprobamate.

That's why probably they are -- we don't know through the data through the numbers. We cannot know if both drugs were taken or because both drugs were detected in blood. That's the way they were reported.

MS. FALKOWSKI: Just a follow-up question. I'm trying to ascertain with a raw number of 45 per year, it's hard to determine if that's a trend line in the absence of, well, maybe all ME deaths went up incrementally during that same time period. And that's what I'm looking for. And I couldn't locate that. It seems relevant.

CHAIRMAN SCHNEIDER: Dr. de Wit?

DR. de WIT: I guess I'm curious that one of the primary motives for -- I'm not sure whether to call it abuse -- suicide attempts. And is that really in the spirit of our scheduling decisions, a drug that has potential for suicide? Are we considering that a drug of abuse?

DR. CALDERON: I think that Dr. Wright

would like to --

CHAIRMAN SCHNEIDER: Dr. Wright?

DR. WRIGHT: Dr. Wright.

Whether it is proper to do so in the spirit of behavioral pharmacology, we don't know, but we found an association between drugs of abuse and suicide attempts. So we have used it as a marker but not as a pathomneomonic marker of abuse-related deaths.

CHAIRMAN SCHNEIDER: Yes, Dr. Klein?

DR. KLEIN: I would just say that it's not a primary indicator. It's associated with drug abuse. And so we mark it like Dr. Wright had said, the secondary issue that we're looking at.

CHAIRMAN SCHNEIDER: Any other questions?

(No response.)

CHAIRMAN SCHNEIDER: Thank you very, very much.

DR. CALDERON: Thank you.

CHAIRMAN SCHNEIDER: Now, Committee, I have a couple of options for us. I would like to suggest that we take a five-minute break and then come back for our discussion and conclude after our discussion. Dr. Wright?

DR. WRIGHT: I do have a piece of

information for you, and that is that there is no scheduled NIDA speaker that we know of.

CHAIRMAN SCHNEIDER: Yes. Thank you. I have been informed of that, and I appreciate that. Is that okay or do you want to forge on without a five-minute break? Being older, I heresy declare a five-minute break.

(Whereupon, a recess was taken at 12:46 p.m.)

A-F-T-E-R-N-O-O-N  S-E-S-S-I-O-N

(12:56 p.m.)

CHAIRMAN SCHNEIDER: If we may, ladies and gentlemen, take our seats, we would appreciate it. My character is being assaulted over here.

Ladies and gentlemen, thank you for convening again. And, Dr. Wright, I do appreciate your willingness to forge ahead.

DISCUSSION

CHAIRMAN SCHNEIDER: We have a question, and that is: What further information and what other data do we believe needs to be gained and brought forth to make a final consideration of the issue?

Let me make a couple of comments to start with, if I might. I certainly do appreciate the industry's input. I do come from a rather -- I don't think I can say biased but experienced person in having dealt in the addiction field for all these many years and having seen what I have seen, specifically with this drug and with other drugs that originally were not considered to be addictive and which down the road were proved to be.

I am prepared to say that I am going back and bring you more information as I review the literature and our own experience of just one small,

and I say small, clinic, 20 beds. And I will peruse literature from 1990 through '94. I've already done the '95 and '96 and have come up with some data. So I must say that I have an experiential bias in this matter.

Secondly, we have heard today from the industry that only a small proportion of the material breaks down into meprobamate, but we have also had evidence to show us that meprobamate will be accumulative. And in those patients, particularly who have developed either tolerance or the desire or the need to take more than prescribed doses, this becomes a major problem.

Having said that, I think that the only other thing that I would like to comment on and to reiterate what I already said earlier today, and that is that this drug appears to have gotten into two hands, that into the prescriptive hands, where it's supposed to be, and it appears that it is in the diverted market. So we have to look at it from that aspect.

I suspect, unless somebody wants to make other suggestions, what I'd like to do is -- yes, Doctor?

MS. FALKOWSKI: No. Go ahead.

CHAIRMAN SCHNEIDER: -- that we poll and just go around and make whatever comments we want to make regarding what additional information is necessary to be brought before the department for -- why don't you go ahead and start. You had a question.

MS. FALKOWSKI: That's right, so antsy. At any rate, I guess one of the things that I feel is an important charge of this Committee is to really evaluate the existing data that's available from multiple sources, acknowledging that each data source has its limitations but collectively they paint a picture that would not otherwise exist.

So, in that regard, I remain adamant in getting some additional pieces of data presented in a way that are more meaningful than currently has been summarized in any of the materials we received.

I think one of the key pieces included in that is a more detailed breakdown of the STRIDE data in terms of summary statistics, in terms of helping us distinguish case reports where it's a doctor gone bad or a pharmacist gone bad or whatever to give us some sort of more meaningful quantitative basis to determine the prevalence of the abuse. I think that's extremely important.

In addition to that, while the DEA's

presentation includes indication of abuse and listed on that slide were doctor shoppers, elevated doses, fraudulent prescriptions, we need more information about what the magnitude of that abuse is.

It's one thing to list incidents around the country and because incidents occurred in many state to assume, that it's widespread. But they still could be isolated cases occurring in different geographic regions. And I need more information to sort that out.

In addition to that, when we heard from DEA about Carisoprodol combined with other drugs and it had an overhead there about cocaine and Carisoprodol combinations, another one with heroin, cocaine, and Carisoprodol sold as heroin, what's the prevalence of that? Are these two cases, one case? I'm curious about that.

So I think those, minimally, are the types of data we need. I also think having heard for the first time -- I guess I just have to back up a second to say that we received information. But, yet, when we came today we heard two additional years of information that we did not get in advance. And I think that puts us all at a disadvantage of terms of being in really an informed position to evaluate

things.

Today was the first time I heard about Carisoprodol coming across the Mexican border. That was the nature of my inquiry about where it's manufactured.

I think there are some things that can be done to try to document that in a more deliberate manner, possibly doing something collaboratively with Customs to see if people going across the border with declarations of drugs, keep track of that for a week or a period of time, how many people are declaring Carisoprodol for personal use. Is that a phenomenon that's going on? Are we talking about something else? At any rate, you kind of get my drift.

I think we're also talking about, wherever possible, for all the different data that we've looked at, we're getting, I believe, mixed messages about a change that's occurred or that is occurring about the abuse of Carisoprodol, usually in combination with other opiates.

And if we're to evaluate a change, then don't group all the years from 1990 to 1996 into one lump sum. Let's see what the change is over the years or is there a change? And what's the nature and the extent of the change?

Let me see. Then I also think special attention needs to be directed with the DAWN emergency room data. And I'd also like further documentation of some of the conclusions reached by the DEA in their statement when they said it constitutes -- and I'm referring here to Page 41 of their document when they state that it's a significant abuse problem in California, Idaho, Massachusetts, Mississippi, Nevada, New York, and Washington.

I guess I would like to see the foundation for those conclusions simply because when you look at DAWN data on a city by city basis, for example, there were no mentions of Carisoprodol in New York City DAWN in either 1994 or 1995.

Now, maybe that's an anomaly and maybe we have heard it's more in western New York. That could be something going on. But if it's a significant abuse problem in the State of Washington, it's curious to me that the number of Carisoprodol, emergency room mentions of Carisoprodol, in Seattle actually declined 18 percent from 1994 to '95. So there are some things that I find curious that don't really match the conclusions that have been drawn.

Finally, I'd like to get what I feel some more accurate information about prescriptions that

have been written. What's the frequency of prescriptions over time broken down by year?

I notice in the document we received the number of prescriptions was mentioned and broken down annually, but the numbers that are presented on Page 36 do not match the same figures cited as coming from the same source appearing later in the document, on Page 195. So there are some inconsistencies.

And I also think that in looking at the data that I had available independently, that using those figures, -- I just picked one group to be the prescription figures -- that between 1992 and 1994, there has been a 14 and a half percent increase in the number of prescriptions for it.

And at the same time, emergency room mentions of it have gone up less than 14 percent. To me, that's contrary to establishing a case for increased prevalence of abuse. So those are just a few things that came to mind.

I also would like, Dr. Wright, if you could comment, too, on what precedent there is for scheduling drugs based on the fact that they're typically abused always in combination with another drug.

And before I direct that question to you,

it strikes me that -- and I'm just throwing this out as food for thought for people, but it strikes me that if we're talking about the abuse potential and the rising abuse of different prescription drugs that are used in ways other than are medically prescribed, there could be bigger fish to fry than Carisoprodol.

And I'm thinking here particularly of clonazepam, which has showed up also used by opiate addicts to potentiate the effects of that, also divergent prescription practices for something that was originally indicated in the treatment of brain seizures. And I'm also thinking of flunitrazepam, which has been scheduled as Schedule I in at least four states and another state as an emergency Schedule I.

CHAIRMAN SCHNEIDER: Dr. Wright, do you want to respond?

DR. WRIGHT: Yes. You are perilously close to becoming a subcommittee chair.

(Laughter.)

DR. WRIGHT: And your enthusiasm does you great credit.

We have a problem, and the DEA has a problem. And we don't know how to resolve the problem. Traditionally law enforcement data has been

treated as categorical data. It's been treated as it occurred, not here is the rate of occurrence, here is how many times it occurred in relationship to this other drug, not this is how serious a problem it is. It has been treated usually as it is a crime, it occurred, we should do something about this crime. And that is a reasonable way if you're in compliance law enforcement, essentially police and protection mode of dealing with what happens. It doesn't matter how frequently a crime is being committed. It is still a crime.

From a science and health perspective and in terms of public policy and how much resources we're going to put on this versus how much resources we're going to put on that or in terms of making a relative judgment of how bad a problem is or whether we're getting ahead of a problem, then we need to begin to look at all of the things that you've said, rates, relative rates, relative risk, and all of the concepts of epidemiology that will delineate the magnitude of a problem in that dimension.

We do not yet know how to look at some of this law enforcement data in terms of rates. We simply don't have a validated method that we've used over time.

So if you have thoughts about that, we would very much like to hear them, probably written because that's easier to think these through than on the spot --

MS. FALKOWSKI: Right.

DR. WRIGHT: -- in the Committee.

MS. FALKOWSKI: Well, I think, even in the absence of rates, some sort of categorization to help us distinguish large cases from small cases to sort of categories of pharmacists gone bad, doctors gone bad, to just --

DR. WRIGHT: So what I'm hearing from you is that it is not helpful for you just to know that something is happening.

MS. FALKOWSKI: No. In the realm of drug abuse, so many things can happen. It is not surprising when they do it, you know.

DR. WRIGHT: But it would be more helpful for you to have some standard comparators or some attempt to categorize how bad is it.

CHAIRMAN SCHNEIDER: Yes, that's it, and how bad --

MS. FALKOWSKI: The nature and extent.

CHAIRMAN SCHNEIDER: How bad does it have to be to be scheduled?

DR. WRIGHT: Okay. Now, I can talk a little bit about that. How bad is it to be scheduled? First of all, we have had drugs that have been scheduled as a result of their abuse in combination with other drugs, probably T's and blues. Pentazocine is the best example of that.

There are some general principles on scheduling that vary according to the specific circumstances in which you find yourself. If there is an emergent problem, it appears there is a grave threat to life and health. We can simply schedule first and sort it out later. That is a rational strategy if you have an emerging problem.

If you have a problem that does not appear to be so severe and has been going on for some time and may have hit the threshold, then another strategy that's been used by the Committee in the past is to say: Do you need this remedy or is a lesser remedy reasonable?

We have had companies take voluntary actions, some of which have been effective, some of which have not, to try to deal with the issue.

So part of what we'd like to hear from you -- and we have more members to go -- is: Is this an emergency or is this something where we should try to

craft a remedy? And if we do, what kind of information will we need to craft that?

CHAIRMAN SCHNEIDER: Thank you.

I'm going to -- is this on the same subject or is it going to bring something up? I'm going to ask if Mr. Lloyd would make his comment that I know he has to make.

MR. LLOYD: Thank you.

I'd like to share with the Committee a small and recognized insignificant piece of data. In our State of Arizona, the Board of Pharmacy does operate a fax network warning system that reports bogus phone-in prescriptions, forged prescriptions, prescription pad theft, doctor shopping, and other incidents that are voluntarily reported to the Board of Pharmacy and pretty generally confined to the metropolitan Phoenix area.

I'd just share with you, for what it's worth, a year ago, in January of 1996, our statistics showed that Carisoprodol was number five reported item in a group of about 12 individual drugs that were reported. Those that were ahead of it were hydrocodones, oxycodones, codeine, and benzodiazepines.

In January of 1997, reporting from the

previous calendar year, Carisoprodol moved up to third in those reportings, headed only by hydrocodones and oxycodones. So it made a significant increase in its position in reportings over the last year.

And then I think one of our previous speakers referred to this but may not have specified exactly the origin of it. The National Association of State Controlled Substances' authorities in a resolution at their meeting in November of 1996 indicated their support for scheduling of Carisoprodol in the resolution that they have published.

CHAIRMAN SCHNEIDER: Thank you.

Ms. Cohen?

MS. COHEN: Yes. I have several concerns, but certainly you were most eloquent and I appreciate it. I'm not sure what the company knows and what they don't know. And in terms of the presentation, I hope that you know more than what was presented. And that troubles me greatly.

And, in turn, what kind of information, what kind of inserts, what kind of labeling are you giving consumers? I think we are apart of the process, and we have to know everything there is to know.

And in terms of the HMOs, since they're

scheduled many people in a short period of time, consumers are going to have to get more information to make some intelligent choices. And I'm not sure that they're going to get it if they don't get more information.

I'm concerned about the dependency, the allegations of dependency. I'm concerned about drug combinations. I don't know how much testing has been done. And, all in all, I'm just uncomfortable.

Let's put it this way. If I went in to see a physician because of some kind of problem and they recommended Soma to me, I would be unwilling to take it based on the information that has not been supplied and the information that has been supplied.

I think we have to do much more than we've got.

CHAIRMAN SCHNEIDER: I think I will poll the group. Dr. Strain?

DR. STRAIN: I think there is something of concern here. I think that the basis of this is anecdotal reports and that that's a useful first step for identifying something of concern, but, as Carol has pointed out, it's hard to get a grip on it as far as the data set.

I don't think -- in response to Dr.

Wright's question, I would not characterize this as an emergency. I don't think we've got to do something today, at least not before lunch.

(Laughter.)

DR. STRAIN: But I will agree with what probably everybody in the room will agree with, which is that we need more data and/or, probably and, we need a better analysis of existing data, I think. So I'm again reflecting my peer.

With those points in mind, I have two further comments. One, I think we need controlled studies of this compound in humans. I would like to see abuse liability testing alone and abuse liability testing in combination.

Dr. Harris has commented that we've got the techniques, we've got the technology, we can do this, let's do it. So I'd like to see some controlled studies. And, secondly, I'd like to see better descriptive work coming out of epidemiologic work.

And I'm not sure how this might be pursued, but if, for example, this could be flagged in the DAWN network as something that we want to hear about over the next few reporting cycles or if there's any other small epidemiologic study that might be done or there's some work through the drug use forecasting

system as well that might complement what we've hard so far.

CHAIRMAN SCHNEIDER: Thank you.

Ms. Falkowski, anything else?

MS. FALKOWSKI: Me?

CHAIRMAN SCHNEIDER: Yes.

MS. FALKOWSKI: No. I think I've said enough.

CHAIRMAN SCHNEIDER: Anything else?

MR. LLOYD: I would agree with what Dr. Strain has said, with what Ms. Falkowski has said. And I'd like to suggest one other item that I don't think I'm betraying any confidence in this. I think there was an FDA-Customs joint effort at a border crossing about a year and a half ago where border-crossing individuals either at Juarez or at El Paso were stopped and queried about their bringing drugs back into the United States.

I don't have the data. I have seen the data, but I don't have the data as a result of that query. That did come up today during somebody's discussion about border-crossing drugs.

If that study is a reliable study -- it was a one-day study. But if that was a reliable thing, maybe we'd want to know about that.

MS. FALKOWSKI: I can speak to that a bit. It was a directed study simply to track the frequency of people declaring Rohypnol coming across. And I think they did it for a one-week period.

I guess what I was suggesting was doing it for a one-week period but doing it with Soma or doing it with Carisoprodol just to get a snapshot picture.

MR. LLOYD: The one I saw had about 15 or 20 drugs on it --

MS. FALKOWSKI: Yes, right.

MR. LLOYD: -- in addition to the Rohypnol.

MS. FALKOWSKI: Right.

MR. LLOYD: Okay.

CHAIRMAN SCHNEIDER: Dr. de Wit?

DR. de WIT: It seems to me that we have close to 40 years of clinical experience with this drug. It's been on the market. It's been widely available. And from the data that we have seen, concern about abuse has really only occurred in the last four or five years.

I'm a little concerned about the increase, but I'm wondering whether it could just be an artifact of changes in marketing or changes in reporting.

I think that we do have the information

that we need available, as Ms. Falkowski pointed out. We can look at use particularly over time in the last, say, 20 years and then also in terms of place and also in terms of quantity and relative to other drugs in similar categories, so other muscle relaxants, both scheduled drugs and unscheduled drugs. So I think it looks as though there's some increase in use.

We need to also separate out whether this is general evidence of abuse or whether it's a fad, which could be exacerbated by kind of popular media, the internet or something like that.

So, in my judgment, this is something that we should monitor, but it doesn't seem to be severe enough for us to take a serious action, certainly not as serious as scheduling.

We could consider, for example, adding something to the label, warning physicians that this should not be used chronically, possibly a letter to physicians indicating that there have been reports of abuse.

So I think there are a number of measures that we could take in doing some surveillance. There are measures that we could take short of scheduling a drug, which seems pretty severe in this category of drug?

CHAIRMAN SCHNEIDER: Ms. Cohen?

MS. COHEN: I think that I expressed my concerns. And everybody else has expressed it better than I can. But I find it worrisome with what came from DEA and what came from FDA and the charts that they showed and the different possibilities of what this drug can do.

I would think Robaxin used to be the drug of choice for muscle relaxants for a while. And they found out it didn't work very well. So this might be the next one. I don't know. But I think we need to know a lot more.

CHAIRMAN SCHNEIDER: I'd like to make one more comment because we're looking for additional data. And I've not seen this ever done. That is, I think alcohol and drug treatment programs across the country, particularly in-hospital ones, although they're getting very -- they're easier to poll these days.

They've dropped from 36,000 to about 1,600 beds in this country, the point being to send a letter of inquiry to the treatment centers across the country or certainly a sampling of them, particularly those of us in southern California, where we are near Mexico, where I know the stuff is being brought in, anecdotal,

factual, statistically not very helpful, and find out just what their experience has been in this drug and some of the other drugs. I think that would be extremely helpful. And I think it would be an eye-opener, frankly.

Dr. Young?

DR. YOUNG: Well, I'm going to speak to the preclinical pharmacology of the compound. I found it very difficult to interpret many of the statements, the descriptions about the clinical pharmacology of the compound in the absence of much understanding of much descriptive work of the preclinical pharmacology of the compound.

As Dr. Harris pointed out, much of the material seems to date from the early '60s, many of the animal tests. And I've got a recommendation.

I'm going to before that make a disclaimer that I'm on the Board of the College on Problems of Drug Dependence. I'm going to make a recommendation that this compound be submitted for evaluation through the sedative and stimulant program that the college runs in order to get some information about its psychological dependence potential using some of the modern behavioral pharmacologic techniques, specifically probably drug discrimination techniques,

although I think there needs to be careful consideration about what the appropriate comparators are and potential for sustaining reinforced behavior.

I also am struck by the allegation somewhat late in the presentations today that this compound produces directly physical dependence. And I'm not sure whether or not the CPDD screens include a direct physical dependence liability, but it seems to me that evaluation of the claim that this compound is producing physical dependence needs to be evaluated in the context of some information about how species who metabolize similarly to humans, whether or not they show a profile of physical dependence as well. And I didn't see any information in the background materials presented about that.

So I recommend that the agency work with potentially the sponsor to develop such information about the behavioral pharmacology of the compound prior to identify the context in which to evaluate the compound's effects.

CHAIRMAN SCHNEIDER: Thank you.

Dr. Khuri?

DR. KHURI: My eloquent colleagues, particularly Ms. Falkowski and Dr. Strain, have spoken to my condition and concerns very well. I would like

to add a few things, however.

We're concerned with small numbers here. I'm impressed by that. But we take every number seriously, number one. Number two, we need more numbers with numerators, denominators, trends, as was well-spoken.

I particularly would like to know the experience of my colleagues in New York City of the Office of Alcoholism and Substance Abuse Services, which runs very good street surveillance teams and has very good data with their ear to the ground constantly and often citing trends before they happen nationally.

Unfortunately, I didn't come prepared with those statistics. Blanche Frank, formerly on this Committee, could certainly be addressed as to whether there is new data there.

Particularly, we have over half a million serious drug abusers in New York City. And they're onto something long before we in academe and treatment are. I'd like to gather those statistics before I feel there's a real problem.

I liked Dr. Wright's usual felicitous phrase that perhaps the threshold for access should be raised so that we can gather more data.

I'm also concerned, and not just on this

subject, about the sources of medications which I find increasing in my own patients who are part of managed care, namely they can order a jug of whatever from their managed care pharmaceutical supplier. I don't fully understand this. I think we need to look into it.

Someone came into my office the other day with 500 codeine IVs, codeine 60 milligrams with Tylenol. She said she just called up and got them. But that's something that we certainly should look to when we're counting numbers because an awful lot is going around the dam that way.

Another thing that concerns me is the issue of suicide. We're dealing with small numbers to begin with, but I was struck that 60 percent of this misuse was used in suicide attempts.

It's hard to really control what's used for suicide. We don't control handguns so well or lye, what have you. Often people who are suiciding just use everything that's around. And we know that drug abusers have very high rates of suicide and people in chronic pain situations have high rates of suicide. So this may be an also-ran with that group. But it's interesting to look at that.

So I think, again, we need more numbers.

And I would not be in favor of complete rescheduling at this time.

MS. FALKOWSKI: May I add one more --

CHAIRMAN SCHNEIDER: Yes?

MS. FALKOWSKI: All right. I wanted to respond to your inquiry about the Street Drug Analysis Unit in New York City because I've looked at Dr. Blanche Frank's report from June of '93 on drug abuse in New York City, where she mentioned -- I perused community epidemiology workgroup proceedings from NIDA for the past four years and found in New York City the first mention of it was in June of '93, where a street research unit reported that it was becoming more common among cocaine users and also Carisoprodol and also sold on the street in Queens and Manhattan, which I find curious because this was in 1993. That year in New York City there were only 31 emergency room mentions. And the following two years, there were none.

DR. KHURI: I am aware of that report. And we have a very savvy team. But I'd like to know what's happening between '93 and '97.

MS. FALKOWSKI: Yes. It has been --

DR. KHURI: It would be very interesting to look at because these are really well-trained

people, and they're in the streets.

CHAIRMAN SCHNEIDER: Is there a physiatrist in the crowd by the name of Dr. Michael Kaplan? Would you like to say a few words?

DR. KAPLAN: Thank you very much for giving me a chance to say one other thing.

One of the hats that I didn't mention from before was I used to be at National Institutes of Health also. I was the Director of the Physical Functioning and Performance Program there.

There was an extramural program where we funded research. And in funding research, we also had to evaluate it. There's always a question for more data, more preliminary information.

I think one thing as a clinician that I'm concerned about is there's always more data that you need and always more preliminary data. When is enough data important? How many deaths do you really have to wait for before it becomes an emergent problem?

I think from listening to people, everybody understands that there is a problem. The magnitude of the problem may not be understood, although it seems to be enough of a problem to bring us together. So I don't think any deaths are really an appropriate thing.

We have the Arizona experience, where you have data there that shows it's a drug of misuse in high numbers. We have a lot of clinical experience. And who pays for the research?

By the time we wait for NIH to put out a proposal or a request for proposals, we get proposals in. We have years. Then the project to be done takes five to ten years.

Do the drugs companies pay for these proposals? Do we wait for NIH to pay for the proposals? I really don't think that we should wait. I think that it should be a classified drug, too, because one death is too many. But it's many more than that.

And then if data supports later on that this shouldn't be classified, you can even make it an over-the-counter drug if you needed to, which would be totally ridiculous.

There's an emergent problem now that really needs to be addressed. Waiting to count people across the border is something that we don't need to do at this point.

CHAIRMAN SCHNEIDER: Thank you.

Are there any other comments from previous speakers?

DR. RAINES: Just for a moment. One of the things that I do with our students at the end of our --

CHAIRMAN SCHNEIDER: Identify yourself.

DR. RAINES: I'm sorry. Arthur Raines, Georgetown University.

One of the things that we do with our students at the end of the course is give them a list of the top 200 drugs that are prescribed because it sort of gives the students a warm feeling that we haven't been wasting their time for the past 9 months.

I was surprised to learn that Carisoprodol was on that list of top 200 drugs. It was something like 180 or some such thing. It hadn't been on the list the year before. And I have not yet seen the list for 1996, which is published in the February issue of one of the drug trade magazines.

I think the data Dr. Calderon showed that between 1990 or '91 and '95 the number of prescriptions has gone up by 60 percent addresses to some extent the issue that was raised a little earlier. And that is: How big is the problem? Is this really a problem?

I think the fact that the apparent abuse of Carisoprodol, which has only been something in

recent times, the last five years, sort of seems to go in parallel with the increase in prescriptions for the agent. And from everything that I have read, most of the individuals that become involved with this drug get it through legitimate medical sources.

So I don't know that the street is going to be a major source of great new insights because that's not where most people are getting their medication. Apparently they're getting it through prescription.

So my subjective impression is we're not dealing with a -- this is not penicillin for pneumococcal pneumonia. We are dealing with a drug which, at best, has modest effects, if any. This would not be a great loss to the medical community if --

CHAIRMAN SCHNEIDER: These are opinions. And I appreciate it.

DR. RAINES: I said subjective. These are my opinions that if the threshold were raised for availability, this would not be a tragedy to befall the medical community.

CHAIRMAN SCHNEIDER: Thank you, Doctor.

Dr. Khuri?

DR. KHURI: I just wanted to correct a

misunderstanding that we get information from our street surveillance on prescription drugs and prescribed drugs but how they're then used by drug abusers and what feels good.

For example, clonidine has been mentioned as an abused drug today. And one that wasn't mentioned is Elavil, amitriptyline, which is extremely commonly used and has a street value as well as a lot of the other antidepressants. I won't go through the long list.

CHAIRMAN SCHNEIDER: Dr. Staats?

DR. STAATS: Thank you for recognizing me. Again, I'm Dr. Peter Staats.

I'd just like to make the comment that I don't think anybody has suggested that there may not be a role in acute management, at which time patients are seeing their physicians.

The industry has indicated earlier that they would be willing to look how many repeat prescriptions are made for this drug. That would give us an indication of what kind of problem this is in the chronic population, which I agree that we don't know. But it should be easily available.

CHAIRMAN SCHNEIDER: Thank you.

Any other comments from the panel, from

FDA? Dr. Wright?

DR. WRIGHT: Well, I think your comments have actually from our perspective been a howling success. I have two pages of things that could be done. We will now have to sit down and sort out with the sponsor what is reasonable to do, what is rational to do, and what is accomplishable.

I would like to review the bidding a little bit so that I can make sure that I've captured those things that you have suggested.

I heard a number of things, most eloquently actually, from our consumer representative that could be done about patient and physician information, ranging from information in the labeling of the drug through physician educational materials, changes in detailing, public information and education programs, and even changes in advertising and promotion, if appropriate.

I heard a large number of things; in fact, too many to go through line by line, that fall under the category of better information gathering, sometimes simply reanalysis of the information that we already have in a denominatored fashion.

I heard a variety of suggestions for some new science that it would be appropriate to do. And

I would concur with most of those, if not all of them.

It was also suggested that a concerned and responsible corporate sponsor would wish to engage in some sort of control activity independent of scheduling to try to deter usage, misuse of their product.

And so we have something in all of those areas. And I think we have what we asked you to do.

CHAIRMAN SCHNEIDER: Thank you.

I would like to take this -- did I hear somebody groan?

(Laughter.)

CHAIRMAN SCHNEIDER: I would like to take this opportunity to thank Ms. Kimberly Topper for her great care of our needs.

(Applause.)

CHAIRMAN SCHNEIDER: Now, unless there is other material that anybody would like to talk about -- yes, Dr. Wright?

DR. WRIGHT: Very brief. So don't feel distressed.

We will be probably trying to put together the subcommittee on outcome measures in tobacco usage trials that was reiterated in this Advisory Committee that we really did need to look at how we collect

those metrics. And so we will be getting in touch with some of you for further opportunity for service.

CHAIRMAN SCHNEIDER: Fine. I would entertain from the Committee unless there's some resistance to this a motion to adjourn.

DR. STRAIN: So moved.

MS. COHEN: I so move.

CHAIRMAN SCHNEIDER: All in favor?

(Whereupon, there was a chorus of "Ayes.")

CHAIRMAN SCHNEIDER: Have a safe trip home, family. Thank you. It's adjourned.

(Whereupon, the foregoing matter was concluded at 1:40 p.m.)